American Journal of Obstetrics and Gynecology

VOL. 69 MARCH, 1955 NO. 3

Transactions of the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia September 9, 10, and 11, 1954

LEST WE FORGET*

Presidential Address

HERBERT E. SCHMITZ, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the Stritch School of Medicine, Loyola University)

WHEN the Fellows of the Association honored me by election to the presidency, my desire was to pay homage to the past and present Fellows who have by their efforts made this such a distinguished society. It seemed appropriate to review their contributions toward solving one major problem of special interest to me: carcinoma of the cervix.

In the first volume of the *Transactions* of this Society we find an invitation to a number of gentlemen interested in abdominal surgery, obstetrics, and gynecology, residing in various parts of the United States, to meet and consider the propriety of organizing under a common name for the purpose of cultivating and promoting knowledge in these several branches of medicine. This brought them together at the Niagara Hotel, Buffalo, New York, on April 19, 1888.

The meeting was called to order at 10:30 A.M. by Dr. A. Vander Veer of Albany, on whose motion Dr. W. W. Potter of Buffalo was elected temporary secretary.

The secretary then called the roll of those who had responded favorably to the invitation, as follows:

*Allen, Henry B.	Baldwinsville, New York
Baker, Washington H.	Philadelphia, Pennsylvania

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

*Banta, Rollin L.	Buffalo, New York
Beckwith, F. E.	New Haven, Connecticut
*Boyd, James P.	Albany, New York
*Carstens, J. H.	Detroit, Michigan
Carson, N. B.	St. Louis, Missouri
Cushing, C.	San Francisco, California
Dunham, J. M.	Columbia, Missouri
*Hill, Hampton E.	Saco, Maine
Ill, Edward J.	Newark, New Jersey
Jarvis, George C.	Hartford, Connecticut
*Lathrop, Thomas	Buffalo, New York
Maxwell, Thomas J.	Keokuk, Iowa
*Miller, A. B.	Syracuse, New York
Montgomery, E. E.	Philadelphia, Pennsylvania
Myers, W. H.	Fort Wayne, Indiana
*Opie, Thomas	Baltimore, Maryland
Price, Joseph	Philadelphia, Pennsylvania
*Potter, William Warren	Buffalo, New York
*Stanton, Byron	Cincinnati, Ohio
Shepherd, George R.	Hartford, Connecticut
Storrs, Melancthon	Hartford, Connecticut
*Taylor, William H.	Cincinnati, Ohio
*Townsend, Franklin	Albany, New York
*Vander Veer, Albert	Albany, New York
Wathen, William H.	Louisville, Kentucky
Webber, N. W.	Detroit, Michigan
*Werder, X. O.	Pittsburgh, Pennsylvania.

The names of those present at the meeting are preceded by an asterisk.

Telegrams or letters of regret were received from Drs. Ill of Newark, Maxwell of Keokuk, Myers of Fort Wayne, and others, who pledged their cooperation and support of the objects of the meeting.

On motion of the Secretary, Dr. Thomas Opie of Baltimore was elected temporary chairman.

The transactions of this organizational meeting include a presentation by William H. Wathen entitled, "Hysterectomy for Malignant Diseases of the Uterus." The author pointed out that the mortality for the abdominal approach for uterine malignancy was too great, but that the mortality could be reduced to 8 to 10 per cent by means of the vaginal route in selected cases. He further stated that some physicians denied the value of surgery for cancer, among them A. Reeves Jackson of Chicago. Continuing with his observations the essayist stated that most gynecologists agreed that the operation was contraindicated if the tumor had extended beyond the uterus. He pointed out that even though cases are suitable for surgery, only men properly trained in the technique should attempt it.

When the diagnosis of cancer is doubtful, he advised biopsy and examination of the tumor tissues thus obtained. Even, then, however, he continued, it is not always easy to make a correct diagnosis. "Whether invasion is beyond the confines of the basement membrane or whether it has merely invaded a gland is sometimes a moot question."

He then spoke of preoperative preparation, including deflation of the bowel and cleansing of the vagina. He concluded with a description of his operation —separating the uterus anteriorly and posteriorly, and then applying large clamps to the broad ligament, excising the uterus, and leaving the clamps in place.

Since that time, Fellows of the Association have contributed much to the control and treatment of pelvic cancer. *Lest we forget,* I have reviewed the writings of the Fellows of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons on cancer of the cervix from the time of the organization to the present.

Beginning with the Charter Fellows, we find Vander Veer interested in the management of cancer of the uterus complicated by pregnancy. He found the incidence to be once in every two thousand pregnancies with infant survival of only 20 per cent, and immediate maternal survival of 50 per cent.

Cases of cancer of the cervix uteri, associated with pregnancy, were divided into three groups so far as treatment was concerned:

Group I.—Those cases in which the disease is confined to the uterus and the size of the uterus is not more than that of a four months' gestation. Immediate vaginal hysterectomy was advocated.

Group II.—Those cases in which the carcinoma is confined to the uterus but in which the size of the uterus precludes vaginal hysterectomy. For all of this group he advised "extirpation of the uterus by Freund's method as modified by Zweifel."

Group III.—This group comprises all cases of any period of gestation where total extirpation of the uterus is impracticable. For these cases he advised Porro's supravaginal hysterectomy, to be followed by complete extirpation of the cervix.

Vander Veer admitted that carcinoma might occur in the stump of the cervix following suprapubic hysterectomy, but did not believe that routine total hysterectomy was indicated because the dangers of total hysterectomy were greater than the risk of carcinoma occurring secondarily in the cervical stump if treatment were prompt. If the cervix had to be removed, the vaginal route was preferred. He cautioned that routine pathological examination of all myomatous uteri should be done, as many unsuspected cancers of the uterus and cervix would be discovered and proper treatment instituted.

J. H. Carstens advised teaching women the symptoms of cancer and seeking advice early. He stressed that cancer is local at first and can be cured if treated promptly. The three most important symptoms he listed as bleeding, discharge, and loss of weight. He insisted that thorough physical examinations and curettage, as well as education of the women of menopausal age, were necessary. He admonished his colleagues not to throw away the curettings obtained at diagnostic curettage but to examine all curettings microscopically. Although the "cancer age" is 35 to 40 years, he taught that younger patients can have cancer. He cited several instances of cancer in patients under 30 years of age. Carstens further stated that one woman in eight dies of carcinoma and suggested the following:

1. Publicity such as is common in tuberculosis.
2. Careful evaluation of every case of leukorrhea.
3. Careful following, in every case of abnormal bleeding, by examination, diagnostic curettage, and microscopic examination of the curettings.
4. Diagnosis before onset of pain, which is a late manifestation of carcinoma.
5. Investigation of every case of loss of weight or pain in the back for a possible genital carcinoma.

E. J. Ill discussed the differentiation of the history, signs, symptoms, and findings in the menopause and carcinoma of the cervix and uterus, and re-emphasized the importance of early diagnosis. He further stated, "The microscope can rarely be relied on in the examination of curettings. It will often mislead and will be of value only when it gives positive results in connection with other

symptoms.'' The author stated that only one in five of all of his cases of carcinoma was early enough for operation, and only 25 per cent of the patients operated upon remained free of recurrences.

In a later report in opposition to the widespread practice of hysterectomy for fibroid uteri performed because of fear of malignancy, Dr. Ill reported findings in his private practice for eighteen years. From autopsy findings he determined the incidence of fibroid tumors in all women as being between 4 and 8 per cent. In operating upon 443 women for fibroids he did not find any malignancy. These cases were from a group of 2,600 women with fibroids observed in his office; therefore, his operative incidence was 17 per cent. At the same time, 580 patients with carcinoma of the uterus and cervix came under his attention. Of these, 175 were operated upon and at operation only 5 showed fibroids, an incidence of 2 per cent. Dr. Ill reasoned thus: ''All women have an incidence of fibroids of 4 to 8 per cent. Only 2 per cent of my cancer patients showed fibroids. Therefore, there is no definite association between fibroids and malignancy.''

In his last publication on this topic, the following conclusions were drawn:

1. Cancer of the corpus which is limited to the uterus should be treated by hysterectomy.
2. In cancer of the corpus which has gone beyond the uterus, radiation followed by hysterectomy was the choice.
3. In cancer of the cervix he felt that the true statistics showed radium to be the best cure. Although most authors at that time disagreed, he cited many statistics to prove this.

A. B. Miller reported the case of a woman who was kicked in the left inguinal region and in whom a carcinoma of the cervix was found one year later. The point the author emphasized was the promptness with which malignant disease often follows trauma or chronic inflammation.

E. E. Montgomery, as early as 1894, advocated the use of sacral resection as an approach for the removal of all malignant tissue whenever carcinoma of the cervix involved the rectum and parametria. Previous to this operation he performed a colostomy. He used the abdominal operation only when conditions for the vaginal approach were not fulfilled. ''It allows for a wider excision of parametrial tissues, including, if necessary, the bladder.'' He wrote extensively on the value of educating the public relative to the early symptoms of cancer and believed that there was a vulnerable tract running through families making them susceptible to carcinoma. He preferred the vaginal approach and frequently described his operative technique of employing clamps. In a report of his surgical cases for the year 1887, the following case is included: A 50-year-old married woman with a history of hemorrhage for several months, leukorrhea, and severe pain in the pelvis, was admitted for ''extirpation of the uterus for cancer.'' The operation is described: ''The cervix was seized with vulsella forceps, cutting through the vaginal walls and pushing up the tissue on all sides. While doing this, the cervix was found so infiltrated it tore off.'' Due to infiltration of surrounding tissue the plan of operation was changed. ''The cervix was cut through at the level of the junction of peritoneum upon its anterior wall. Then the anterior vaginal wall was sutured to the stump of the uterus and the vagina was packed with iodoform gauze.'' The postoperative course was complicated by a strangulated hemorrhoid which was ''cut away.'' The patient was doing well six months postoperatively, and on examination the vagina was free of disease.

In a publication in 1898 Dr. Montgomery divided carcinoma of the uterus into:

1. Disease involving the vaginal portion of the cervix: polypoid, infiltrating, or excavating in character, and described its local spread.

2. Disease involving the vaginal portion of the cervix from the internal os to the external os: infiltrating, cavitary, or combination in character, and described its spread.

3. Body of the uterus: diffuse, circumscribed, and polypoid in character.

He agreed with Emmett that neglected lesions of parturition were a prolific cause in the development of that disease and advocated postpartum examination and the early repair of the parts. For the palliative treatment of patients where the disease affords no hope from a radical procedure, he advised sleeping in a well-ventilated room, keeping the subject in ignorance of her true condition. She should be encouraged to keep about. The diet should be nutritious and sustaining; large quantities of milk and eggs should be its basis. He concluded: "A time comes sooner or later in the life of every such individual when she must resort to opium in some form for relief."

W. H. Wathen published his thinking regarding hysterectomy for malignant diseases of the uterus the year this Association was founded. He emphasized the advantages of the vaginal approach rather than the abdominal because of the higher mortality rate of the latter. He insisted that anyone who attempted to extirpate a cancerous uterus should be fitted to do so and know well its indications. He felt that even the pathologist did not always find it easy to differentiate between a benign growth and cancer. He listed the four conclusions of Furst as to when to extirpate a uterus although the anatomical diagnosis was benign. Case reports of patients suffering from carcinoma made up his remaining publications.

X. O. Werder in 1898 described a new operation for the radical treatment of cancer of the cervix, consisting of the removal of the uterus and vagina "en masse" by the suprapubic method. He felt that previous techniques left too much of the vagina, which was the first tissue invaded by cancer of the cervix. Therefore, after he had the uterus freed, he stripped the anterior vaginal surface from the bladder and urethra and the posterior surface from the rectum. He then pushed the uterus and upper two-thirds of the vagina through the vaginal outlet and peritonealized the abdominal cavity. The vagina and uterus were then amputated from below. The other advantage besides getting more of the vagina, he stated, was that the vaginal tube was not opened and therefore there was less chance of inoculation with cancer tissue. Two years later Wertheim described this as his original operation. Then, still later, he added the node resection. By 1905, because morbidity and mortality were too high following the abdominal hysterectomy with wide excision of the vaginal cuff, and impressed by the Byrne operation, Werder modified the technique of vaginal hysterectomy as follows:

1. All dissection of the cervix from the vagina, bladder, and rectum was done with a hot cautery knife.

2. When anterior and posterior peritoneum was opened, the uterus was clamped and removed. These clamps were reclamped with Dawnes' electrothermic clamps and cauterized. He felt that the cautery destroyed some of the parametrial extension.

In later reports he again described the technique of the Byrne operation which he preferred to the Wertheim procedure. He maintained that the latter was nothing more or less than the procedure he first performed and described. Analysis of his material established the ratio of malignancy of the body to carcinoma of the cervix as 1:4. A comparison of his results with those of the Wertheim Clinic report of that time embodying 185 cases with 13 recurrences

or 7 per cent, and 42.5 per cent cures, showed the author's results in 59 cases of "igniextirpation" to be 27 cases or 45.76 per cent living at the end of a five-year period. Of the 27 patients surviving in this series, 8 or 29 per cent had recurrences more than five years after surgery. The difference in per cent of late results following these two methods, he explained, was due to the more unfavorable material dealt with as compared with that of the large European clinics. It also must be accounted for, he continued, on a larger portion of lymphatic involvement due to the more advanced stage of disease at the time of surgery, and therefore by the cautery method only a small amount of the regional glands likely to become invaded could be extirpated. The Wertheim technique, he agreed, will get more of the regional spread.

As we leave our founder members, we find *T. B. Eastman* teaching that two conditions seem to stand in a conspicuous etiological relation to cancer of the uterus. In discussing the histopathology of hyperplastic endometritis he developed the concept that malignant disease is the result. He maintained that neglected lacerations of the cervix constitute the most important factor in the etiology of cancer of the cervix. Many of the leading gynecologists of the time (1900) are quoted, all giving evidence to the fact that the malignancy was relatively rare in nulliparous women.

C. C. Frederick reviewed 500 hysterectomies for cervical carcinoma and found that only twelve of the patients had lived five years or more. In his own series of 26 patients who seemed operable, he performed 14 hysterectomies and 12 high amputations of the cervix. Only one patient lived over five years—this patient was treated by hysterectomy and lived seven years.

He felt that since the results of hysterectomy had been so unsatisfactory, he was justified in performing high amputation because the operative risk was greatly reduced and, in his experience, the results were as good as with hysterectomy. He felt that hysterectomy per se, either abdominal or vaginal, was an incomplete operative procedure for carcinoma. He quoted the work of Dr. Baree who said that 80 per cent of all carcinomas of the cervix are inoperable. He pointed out that the results of cancer treatment in Germany were better because people there were trained to consult the surgeons early. He wrote extensively on "How can we best educate women to seek relief early from cancer of the uterus?" In a later publication he advocated the use of the cautery for early carcinoma of the cervix without invasion, as done by Dr. John Byrne of New York. The latter had reported a series of approximately 100 cases with the following results: 10 patients who survived two years, 11 over three years, 6 over four years, 8 over five years, and 6 over seven years.

P. Findley, speaking before the Chicago Gynecological Society on Jan. 17, 1902, presented a case of a nulliparous woman passing into the menopause with a cauliflower growth on the cervix. He presented this case because the woman had never borne children and had never had any cervical dilatation; it was the first such case he had ever seen.

However, Watkins, McArthur, and Emil Ries all commented that the condition was not rare and that they felt that there was little or no evidence that lacerations of the cervix bear any relation to carcinoma. Findley wrote on primary malignant tumors of the infant uterus and reported 33 cases in detail. In discussing carcinoma of the uterus, he felt that prophylactic measures could prevent 90 to 95 per cent of all carcinoma of the cervix. He believed in educating women to recognize the early symptoms. He stressed that pain and weight loss were late symptoms and that some cases were completely without symptoms. Although he reported two cases in which the entire carcinoma was removed with the curet, he did not think curettage alone was good treatment. He later wrote that carcinoma of the cervix was more common in women of middle age who have borne one or more children. He believed

that 60 per cent of carcinomas arise ten plus years after the last childbirth and 20 per cent arise twenty or more years after childbearing. This suggested to him a probable relationship between pathological conditions present in the uterus conducive both to sterility and carcinoma, e.g., erosions, endometritis, eversions of the cervix.

In discussing erosions and eversions as precancerous lesions, he quoted Ewing and agreed with him that "when atypical hypertrophic and hyperchromatic cells are growing downward from the epidermis or fill enlarged gland alveoli, the diagnosis of beginning carcinoma is justified." His last communication contained the following statement: "My own experience is for irradiation and irradiation only."

O. J. Polak, as early as 1902, drew the following conclusions in an article entitled, "The Early Diagnosis of Uterine Cancer: Operative Limitations":

1. The early diagnosis is possible.
2. The earliest symptoms differ, depending upon whether the disease begins during menstrual life or after the menopause.
3. During menstrual life every bleeding should be compared with what it has been in the same woman. Be suspicious of intermenstrual spotting and serous discharge.
4. After the menopause, any serous or sanguinous discharge is significant.
5. Every woman after thirty who may exhibit any menstrual vagary or persistent leukorrhea, should be examined.
6. Radical operations should be limited to those cases in which the disease is confined to the uterine tissues.

A few years later he re-emphasized these observations and described several stages of cervical carcinoma: first stage, a flat nodule; second stage, moderate disintegration of the cervix; third stage, extensive involvement of the cervix and vagina. Adenocarcinoma of the cervix, he stated, was located deep in the cervix. In closing, he asked that every woman be examined during her menopause.

In another report we find Polak advocating total hysterectomy for benign uterine disease because of the danger of carcinoma occurring in the stump after supracervical hysterectomy. He found 900 cases of fibroid tumor reported in the literature treated by total hysterectomy with undiagnosed carcinoma of the cervix which, if subtotal hysterectomy had been done, would have been left to cause the death of the patient. Mortality comparison of the total and subtotal hysterectomy, he stated, was 2 per cent to 1.5 per cent. Therefore, he concluded, the risk of the more complete operation does not equal the risk of leaving behind carcinomatous tissue or at least tissue in which carcinoma is likely to occur at a later date.

In a publication in 1928 Polak discussed sensitivity and resistance of squamous-cell carcinoma and its influence on selection of treatment. He believed that the present understanding of the routes of extension indicated that Group I cases are treated best by surgery and all others by radiation. In 1931 his conclusions were: The best treatment for cervical cancer is radiation treatment; surgical treatment of cervical cancer should be abandoned since better results can be obtained by radiation. The woman is better off with no operation than with an incomplete operation.

I. C. Rubin stressed the import of microscopic study of all tissues removed at surgery. In histological study he emphasized the importance of: (1) indistinct cell outline, (2) irregular and large deeply staining nuclei, (3) no definite stratification, (4) marked nuclear granulation.

He was less concerned with mitotic figures. The changes in the epithelial cells themselves he believed more important diagnostically than the actual depth

or extent of epithelial invasion. The best hopes for early detection of cancer he listed as: (1) careful routine clinical examination, including bimanual and speculum examination, sounding of the uterus and, if indicated, cervical biopsy and dilatation and curettage; (2) careful routine pathological examination of all curettings.

In 1914 Rubin reviewed the beginning use of radium, mesothorium, and x-ray. He then discussed 18 patients operated upon by Wertheim in which one of the above agents was used prior to surgery. In all instances, the tumor diminished in size. Small cancer rests remained in 16; 5,000 mg. hours of radium was used for a small lesion of the anterior lip of the cervix in one, and this was the only complete cure.

He stated that much work still had to be done, but that these agents were not ready to replace surgery until they cure more than the superficial epitheliomas.

In other publications Rubin gives an excellent résumé on the pathology of cervix cancer, mentioning modes of propagation, types of carcinoma, frequency of carcinoma growth according to location, incidence of necrosis and ulceration, and involvement of parametrium and lymph nodes. Regarding pathogenesis, he states that Virchow's irritation theory holds as proved by coal-tar experiments with animals and correlates this in the human with erosion of the cervix due to trauma or childbirth or chronic diseases such as gonorrhea or tuberculosis.

J. H. Jacobson compared the reports of continental operators with those of the Americans and concluded that it was apparent that the best results in the surgical treatment of uterine cancer were obtained from the radical abdominal operation. He collected 2,765 radical abdominal operations from the literature and personal communications in a statistical study. The report of this study was made to the Gynecological Section of the American Medical Association at its meeting in St. Louis, June, 1910.

In this report it was shown that the average operability by the radical abdominal operation of all patients observed was 65.17 per cent; that the average general primary mortality was 19.94 per cent; that the permanent cures five years after operation in the hands of five different operators were 40.72 per cent, while the absolute cure of all cases observed during a period of from two to six and one-half years after operation in the hands of five operators was 21.14 per cent. It was shown that a greater familiarity with the surgical method not only reduces the operative mortality but increases one's own operability rate as well. From a review of the literature for the various procedures employed in performing the radical abdominal operation he listed the development as follows:

Engebeck (1813)

Sauter (1821)

Czerny (1878) advised the vaginal approach for cancer of the uterus. The vaginal approach was also championed by Billroth, Mikulicz, Olshausen, and Schauta. Werde combined the abdominovaginal approaches and both Pawlek (1888) and Kelly (1892) used ureteral catheters to identify the ureters and avoid damage.

In 1878 W. A. Freund of Breslau successfully performed the first abdominal hysterectomy for carcinoma of the uterus. Ries (1895) described the following procedure in a carcinoma of the portio:

> "The cancerous tissue is cut and scraped away, the bleeding surface is thoroughly cauterized and shut off by flaps of the vaginal wall which are sewed together over the os. The patient is then put in Trendelenburg position; removal of the uterus, ovaries, tubes, and broad ligaments is carried out. Then taking the bifurcation of the common iliac artery as the starting point, the peritoneum is cut open on

the posterior wall of the pelvis and the glands are dug out with the surrounding connective tissue by the sole aid of the fingers. The peritoneum is closed with sutures.''

Clark in 1895 introduced the ureteral bougies and advocates the excision of a much larger portion of the vagina than usual. He showed that 50 per cent of patients with uterine cancer had lymph glands with disease and they could be removed only through the abdominal approach. Pryer (1896) advocated the ligation of both internal iliac arteries. ''My object,'' he stated, ''is to remove all the tissue I can and what I cannot I want to starve.''

Mackenrodt in 1901 advocated the extraperitoneal principle of the operation, followed by Amann who in 1902 modified it by dissecting free the vesical artery and protected it as much as possible, exposing the ureters and finally covering them up, instituted drainage with glass or rubber drains laterally along the vagina through the labia. C. O. Jormes, in 1904, disinfected the vagina two or three days prior to the operation by using abundant douches of potassium permanganate and oxygenated water twice daily and tamponing with iodoform gauze after each irrigation. Wertheim in 1907 after a careful preliminary treatment of the carcinoma per vagina by scraping and burning it with a Paquelin's cautery, opened the abdomen through a medial longitudinal incision.

''Then by dividing the posterior layer of the broad ligament expose the ureters up to their entrance into the parametrium.'' ''It is necessary,'' he cautioned, ''to avoid isolating them all around as their surrounding vascular network must be spared as much as possible. After dividing the peritoneum, the bladder must be separated from the uterus followed by ligation and division of the infundibulopelvic, broad and round ligaments.'' He next ligated and divided the uterine vessels with the surrounding cellular tissue.

''As soon as the uterine vessels are divided the vesical portion of the ureters becomes easily accessible and is separated followed by separation of the rectum and vagina. The parametrium is then divided as close as possible to the pelvic wall and the vagina is cut across. Extirpation of the lymphatics up to aortic bifurcation and downward as far as the obturator foramen follows. The cavity created by removal of the tumor is filled in with iodoform gauze down to the vulva.''

Bumm (1909) added the double clamping of the ovarian vessels laterally to the ovary; also the splitting of the peritoneum beginning at the base of the spermatic vessels and making a lateral curved incision anteriorly over the round ligament to the middle of the vesicouterine excavation. Bumm's procedure greatly simplified the operation and had the additional advantage of being bloodless. It separates the two layers of the broad ligament bluntly with faster visualization of ureters and large vessels. Jacobson from the foregoing review of the literature adopted in 1909 the combination of the Bier's spinal anesthesia with Bumm's modification of the Wertheim technique in which the vaginal vault is left open and early postoperative x-ray treatment is started.

J. Van Daren Young in the *Transactions of the New York Obstetrical Society* of the meeting of April 12, 1910, presented a specimen of adenocarcinoma of the uterus removed Dec. 30, 1909, by panhysterectomy. In discussing the points of interest, he pointed out the danger of the curet as a means of positive diagnosis, both for perforation of the wall and the spreading of cancerous cells.

J. N. West in the *Yale Medical Record* of 1905-06 quotes Morris of England as not believing that heredity, injury, irritation, occupation, worry, and nationality are the etiology, but only predispose to cancer. He believed that previous injury is important and recommends repair of all cervical lacerations and injuries. In discussing the three theories of cancer etiology, namely, Thierssch, Meerobic, and Conheim, he supports the latter. He preferred panhysterectomy with pelvic lymph node removal and decried the ultraradical operation, i.e., removing rectum, ureters, bladder, and much connective tissue. He pointed out that at Johns Hopkins from 1885 to 1904 they had a 19 per cent rate of

no recurrence five years following hysterectomy, whereas another single operator reporting 200 cases of cervical carcinoma had "universal record of return."

He wrote at length on lacerations and chronic cervical lesions predisposing to cancer. He cited statistics showing that only 3 per cent of cervix cancers were in nulliparas. He attempted to link parity to cervical disease and then on to cancer. He showed that 74 per cent of cancer occurs after 40, and suggested routine speculum examination after 40. His conclusions were:

1. Periodic health examinations are valuable.
2. Treat cervical lacerations early.
3. In extensive cervical disease, amputate the cervix.
4. Watch polyps closely.

F. Blume stated in the *Pennsylvania Medical Journal* of 1904-05 that the symptoms of the disease in the early stage are too indefinite to render a diagnosis possible without the microscopical examination of a sufficient portion of the diseased tissue.

Thomas Wilson felt that where cancer affects the cervix, examination by the finger, the speculum and sound is usually sufficient. If after usual methods of examination have been employed diagnosis is still doubtful, a microscopic examination of a wedge piece of the tissue should be made.

The same year, writing in the *British Medical Journal* on "Necessity for Immediate Diagnosis in Cases of Uterine Cancer," he insisted that the results of an examination must be conclusive; when any doubt exists, there should be immediate recourse to the microscopic examination of the tissue removed. He stated that for some time after its commencement the disease can be definitely cured in a large proportion of cases by the aid of surgery.

R. R. Huggins in the *Pennsylvania Medical Journal* of 1905-06 supported the theory of chronic irritation as a cause of cancer of the cervix and referred to "conditions in the cervix uteri which may be precancerous." He stated, "It is our duty to treat the matter with due consideration and where we meet with inflammatory conditions of the cervix, such as cervicitis, erosions, unhealed lacerations, we should cure these simple lesions, if possible, whether they produce symptoms or not."

E. Ricketts reported "Phlebitis Following Hysterectomy for Cancer" in the *Lancet-Clinic* of 1908. He recounted the symptoms and the death of the patient on the seventeenth day. Several discussants pointed out that there existed a noninfectious type of phlebitis (phlebothrombosis) which gave a picture similar to infectious phlebitis. There was a brisk argument among the discussants as to the value of early ambulation; one pointed out that the Mayos were ambulating their patients as early as the fifth or sixth day postoperatively, while others staunchly maintained that they would not permit their patients to ambulate until two or three weeks after surgery.

T. Welton wrote vehemently on the disadvantages of using a curette and advised against its use.

E. A. Weiss opposed the Wertheim operation and supported Werder's igni-extirpation. By adding his cases to those of Werder he reported 121 cases with a mortality of 5.8 per cent. Wertheim's mortality he gave as 16.6 per cent. Werder's five-year survival rate ran 45 per cent while Wertheim's figures for five-year cures ran to 53 per cent.

The author did not elaborate on Wertheim's higher survival rate but discussed the chief causes for recurrence and showed why the cautery technique prevented direct implantation of cancer cells and overcomes incomplete removal. In a later report he reviewed the literature and showed that there was a decided

inclination to abandon surgery in favor of radium. In the borderline group a combination of cautery amputation of the cervix followed by moderate dosage of radium was advised.

He used 1,200 to 2,400 mg. hours of radium after high cautery amputation in 15 patients without fistula formation or other bad results. A safe rule, he stated, was to use 2,400 mg. hours of radium because this does not produce a heavy scar, so that if radical surgery was to be done after radiation, the scar tissue would not make the operation impossible.

R. E. Skeel advised early diagnosis through microscopic examination of tissue before signs or symptoms of the disease occur. He believed many cases of carcinoma of the cervix might be prevented if every case of lacerated, eroded, hypertrophied cervix in women past the childbearing age was subjected to high amputation. The radical panhysterectomy should be limited to those cases which are discovered before marked symptoms are present. He favored palliation with radium in late cases.

In a later publication he reserved panhysterectomy for patients in whom a positive diagnosis can be made with the microscope only. In a review of the article Reuben Peterson did not agree. He liked surgery. John G. Clark and W. J. Mayo both felt that radium should be used for all. Howard Canning Taylor felt that if the cancer had not invaded the vaginal mucosa, surgery should be performed; otherwise, radium should be used.

W. S. Bainbridge reviewed the history of cancer and postulated that there is a multiplicity of pathology in cancer. He advocated ligation of the internal iliac vessels as a palliative measure and preferred the surgical treatment of the disease—"the method of cancer control originated by our neolithic forefathers of the flint and hot stone age—surgery."

A. Crotti reviewed the symptoms, classification, diagnosis, and treatment which he believed should be surgical. Therefore he advised alerting the public to early diagnosis.

Louis E. Phaneuf in 1922 reported two cases of early cancer of the uterus treated by vaginal panhysterectomy because medical consultants advised against abdominal panhysterectomy. "The treatment of cancer," he wrote, "is the avoidance of cancer, until we know the cause." Lacerations should be repaired when irritated. Erosions should have linear cauterizations. Chronic endocervicitis may also be healed by cauterization. He wrote again and again that carcinoma seldom attacks a healthy cervix. He did not believe cervical malignancy to be rare in the nullipara, because over one five-month period he observed three such cases. He used x-ray and radium to treat carcinoma of the cervical stump but was dissatisfied with his end results.

J. V. Meigs in 1930 reported on the histological changes produced by radium treatment of cancer of the cervix. In 1937 he outlined the method of radiation treatment at Pondville Hospital and concluded that irradiation treatment of cervical cancer held considerable hope for many women. In 1939 he concluded that the histological grade was of less importance in prognosis than the clinical classification. He observed that regression of the tumor occurred in those patients having a marked rise in the number of mitoses on the third or fourth day following treatment. Following these studies, he and his associates turned their efforts toward the vaginal smear studies. He warned that a negative smear never excludes cancer but advised its use as an adjunct in diagnosis and for screening of large numbers of women. Later, following extensive work with his many colleagues, he concluded: "In cancer of the genital tract, the smear is of help not only in diagnosis, but also in prognosis and in the detection of persistent or recurrent disease."

Meigs, more than any other person, is responsible for the re-evaluation of the surgical treatment of cancer of the cervix. He advised retroperitoneal lymph node dissection following complete radiation therapy, when the results of irradiation are encouraging. Then, dissatisfied with his statistical evaluation and results of treatment of cervix cancer, he began doing "Radical Hysterectomy With Bilateral Pelvic Lymph-Node Dissection." His ability to perform this procedure in one hundred consecutive patients without operative mortality and his results in early cancer in selected cases is the basis of many reports. He has worked consistently to determine in which case to employ surgical means and in which situations irradiation therapy is preferable. In his latest publication he has turned his attention to the "Uptake of Labelled Phosphorus by Cancer of the Cervix."

W. T. Dannreuther in 1925 cautioned that because of the high mortality of Wertheim and Schauta operations, a simpler treatment should be sought for carcinoma of the uterus. He advised that combining radium therapy, both preoperatively and postoperatively, with panhysterectomy in cases that are not too far advanced, may increase the percentage of five-year cures. His pathological studies during therapy revealed the squamous cell growths to be more resistant than the cylindrical and transitional cell types, and in tumors in which both types of cells are present, the squamous cells predominated long after the other cells have disappeared. The clinical behavior of cancer of the uterus under the influence of radium radiation, he found, can be checked by repeated histopathologic examinations. His opinion at this time was that radical operations are unnecessary after thorough irradiation. In later reports, he stressed the desirability of small and slender intracervical radium sources, and advised intratumor transfixation with gold or platinum seeds. He favored preoperative irradiation and then radical hysterectomy in young women.

B. Z. Cashman maintained that chronic cervicitis seemed to be a contributing factor in the causation of carcinoma of the cervix, and wrote extensively regarding the prevention of carcinoma by cautery of the cervix. Deep cauterization, he stated, is an effective method of preventing carcinoma. In a series of 10,000 cases, only two cases of cancer of the cervix are known to have occurred. He believed that deep cauterization of the cervix made total hysterectomy for benign conditions of the uterus unnecessary.

James A. Corscaden reported on the follow-up of 958 patients treated for benign uterine bleeding by the radiotherapeutic menopause. The average follow-up was for 6.7 years each. Of the 15 carcinomas which developed subsequently, nine were of the corpus and six of the cervix. It was inferred that the endometrium of the uteri which bleed abnormally prior to the menopause is predisposed to the subsequent development of carcinoma of the corpus. Prophylaxis against carcinoma of the uterus, he concluded, should be an important factor in a plan of treatment for uterine bleeding prior to the menopause. His interest in pelvic irradiation was intense, and he described procedures for employing irradiation so as to gain the maximum effect. He concludes that 85 to 90 per cent of carcinomas of the cervix are suitable for no therapy other than radiation. By the use of a precision stereoscope, location of radium units can be determined accurately, the distance between them measured, and the dose calculated. By this means a pattern of distribution of radium needles in the cervix and parametrium has been developed which delivers a minimum dose of 10,803 gamma roentgens to the areas indicated. He defended radiation as the treatment of preference for carcinoma of the cervix. He described intestinal injuries after radium and roentgen treatment of carcinoma of the cervix.

Thomas E. Jones reported on cases of cancer of the uterus treated in the Cleveland Clinic to 1925. His conclusion was that cervical adenocarcinoma

demands no variation in clinical recognition or treatment from that of the squamous-cell carcinoma. He felt that these results as given justify the continued use of radiation therapy for carcinoma of the cervix. He defined the radium dose, and reported later on an improved technique of irradiation. In 1931 he analyzed Ruben Peterson's results and concluded that 40.09 per cent of his patients who were operated upon were cured permanently. If this entire group of 380 patients had been treated with radiation, the percentage of cures, he believed, would have been considerably higher. Jones also wrote on benign stricture of the intestine, considering it a rare complication (1.4 per cent) following irradiation, and admonished his colleagues that it should not constitute a retarding influence on therapy.

J. W. Kennedy wrote that injury to the uterus, and especially the cervix, due to changes during pregnancy, menstrual cycle, etc., all cause chronic irritation and help predispose to cancer. The mortality in vaginal hysterectomy is 1 per cent, and therefore the best treatment for cancer is routine removal of the sterile uterus. He believed cervical biopsy to be of value, but stated that nine-tenths of the tissue is not seen. He admonished physicians to repair the cervix in order to cut down the incidence of carcinoma. Surgery, not radiation, is his treatment of choice. He continues, "We do not mean to assume an ignoble stand toward these accepted therapeutic agents in the treatment of malignancy, but we make the statement that we never treat uterine malignancy (confined to the uterus), but always remove the organ." He maintained that biopsy is an injury and the curette a diagnostic and offensive instrument which is responsible for dissemination of disease.

Robert Mussey reported on the experience of the Mayo Clinic with malignant neoplasm of the cervix coincident with pregnancy. He reviewed 26 patients representing 0.7 per cent of 3,570 malignant neoplasms admitted to the clinic between 1909 and 1941. The cure incidence was 33 per cent. The type of lesion, duration of pregnancy, stage of the disease, and recovery rate in each situation are discussed. No definite conclusions could be drawn concerning the relative value of irradiation therapy; however, it appeared that operation is preferable in cases in which the lesion is operable and that supplementary irradiation increases the percentage of good results.

James Young has written a warning that cancer of the cervix can exist as long as ten years before there is clinical evidence of its presence (noninvasive). He pleads for the use of the vaginal smear; and, relative to treatment, states, "The treatment in carcinoma of the cervix rests between radiotherapy and surgery. The overall efficacy has proved to be similar. Either method in good hands has been able to promise a five year cervical cancer survival rate, with freedom from disease in about 25 to 50 per cent of all seen." He believes in an antecedent cell susceptibility.

C. W. Barrett postulated that the epithelial cell proliferation known as cancer is not the disease, but the tissue reaction to an irritant, which may be bacterial, just as the tubercle is a connective tissue reaction to the tubercle bacillus. He advised treating all benign lesions and, if at all suspicious, removing them.

Charles L. Bonifield stated that there were two possible etiologic factors, age and chronic irritation, responsible for carcinoma. The treatment of cancer he divided into four methods: cautery, x-ray, radium, and surgery. He expected further development of x-ray, and stated that radium, though most popular in 1922, was too expensive for wide usage. He said, "Fibroid tumors of the uterus were a penalty women paid for celibacy, and cancer of the cervix was a penalty paid for maternity."

Emil Novak has contributed heavily to the field of tumor pathology, and were it possible to collect all his comments made in the Obstetrical and Gyne-

cological Survey at the conclusion of published abstracts on carcinoma of the cervix, we would find them of inestimable value. His writings are confined to the pathological diagnosis of early cervical cancer, with special reference to the differentiation from pseudomalignant inflammatory lesions. He warns that pseudomalignant pictures are extremely common in the cervix, and as cases come to the gynecologist earlier, there will be an increasing proportion in which the microscope will be essential for making rather than merely confirming the diagnosis of cancer.

In commenting on the recognition of early cervical cancer, Novak warns that although cytology is of value in the screening field, smears in themselves should not be made the basis for treatment. He has described methods of obtaining biopsy specimens, and believes there is still much uncertainty as to the chronological and histological relation between carcinoma in situ and invasive cancer. Dr. Novak stresses the importance of lay and professional education, the need for and means of early diagnosis. He favors radiation therapy for cervical carcinoma because of its lower mortality and equal end results. He reserves surgery for the expert and for radioresistant tumors.

J. E. Davis reviewed 1,700 cervices in order to determine what major changes bear relationship to the development of carcinoma of the cervix. From this he brings out five major points:

1. Benign neoplasms do *not* appear to be of any significance.
2. *Disturbed cellular adjustment* is thought to be a predisposing factor in carcinoma of the cervix.
3. *Endocrine imbalance* is a specific liability.
4. *Trauma* seemed to be a predisposing factor.
5. *Developmental defect* increases the incidence of malignancy.

He concludes, "The same attention given to the cervix that has been directed to the appendix and the tonsils would secure an astounding change in the cancer statistics of the cervix."

H. W. Johnson cited a patient treated by the Wertheim hysterectomy, who survived six years. He reviews the results published by Bonney, and believes this is a tribute to the surgeon and to this method of dealing with malignant disease of the cervix.

C. Duncan irradiated his patients and then modified Taussig's procedure by implanting radon seeds in the lower uterine segment, broad ligaments, and each uterosacral ligament. He removed all retroperitoneal fat exposed since it might contain small lymph nodes.

J. G. Baldwin wrote of the Detmoid method of controlling inoperable hemorrhage. Tourniquets are applied on all extremities to stop the venous circulation but not the arterial circulation. These would then be released slowly. The objective was to increase the clotting elements.

W. H. Vogt discussed the time of appearance, etiology, pathology, state of the disease, using the Geneva classification, and diagnosis and prophylaxis of carcinoma of the cervix. No treatment was discussed.

J. R. Miller detailed a case of carcinoma of the cervix at eight months' gestation, treated by cesarean section and immediate modified Wertheim hysterectomy, with good primary results for mother and baby. He stated that the technique of the Wertheim operation is becoming a lost art in this country, much to the detriment of such emergencies as this case presents.

D. B. Ludwig reviewed 284 cases treated between the years 1921 and 1938. He treated all but 24 with radium and x-ray and gave pertinent facts as to age, stage of the disease, and previous work-up. He found that the further the disease had progressed, the lower the results of cure. He was convinced that estrogen therapy is not carcinogenic. In another report he discusses a case of cervical carcinoma in a girl of 16 years.

E. A. Schumann introduced direct intra-abdominal irradiation in advanced carcinoma of the cervix. After application of radium to the cervix, the patient is placed in the Trendelenburg position, the abdomen entered, and Balfour retractors used. The intestines are carefully packed away. All pelvic tissue except that involved in malignant growth is protected from irradiation by being covered with sheet lead 2 mm. in thickness. "The patient is then taken to X-ray where she is given a full therapeutic dose."

A. P. Leighton believed that radium was the preferable method because patients had remained cancer free for fifteen years after radium treatment. He considered adequate radical surgery too expensive, as the patient must travel far at great expense to the center where only a few men have the training and technique to perform such surgery. He stated that radium is not only palliative, but curative. In adenocarcinoma of the cervix he advocated postirradiation radical hysterectomy.

L. Fraenkel compared the German and American viewpoints regarding operation or irradiation. He credited Freund with performing the first operation for carcinoma of the cervix (1876). He stated that Emil Reis demanded and accomplished the removal of the regional lymph nodes in the pelvis. Fraenkel advised radiation only, and radiation plus operation, but never operation only. Carcinoma in young women and in pregnancy should be operated upon. His reasons: tumors may be refractory. If both methods are at hand, why choose one?

W. A. Scott stated: "With good radium treatment, Stage I and II lesion patients should have 35 to 40 per cent chance of being alive and free from occurrence at the end of five years. This is all the greatest surgical skill can offer, and can be obtained with practically no operative mortality and a minimum of suffering compared to radical surgery. Of the Stage III and IV type lesions, only five to ten per cent can hope for a five year cure. All of these would perish if radium were not available."

C. H. Davis advocates use of the colposcope in early diagnosis and treatment of minor cervical lesions with electrocautery, while lesions in older women require amputation of the cervix or total hysterectomy.

N. P. Sears believed the diagnosis of early cancer of the cervix was only possible if patient, physician, and pathologist cooperated closely. Biopsy, he stated, is simple and harmless if done properly and should be carried out whenever an area suspicious of cancer is found in the cervix.

Q. U. Newell pointed out that both surgery and irradiation have shown about equal results in the treatment of cervical carcinoma but he preferred to use surgery in the management of early carcinoma. Five years later he stated that his treatment for carcinoma of the cervix was radium. Improvement of technique resulting in improved results produced this change in his thinking. He discussed dosage and cautioned that these agents should be used by the skilled only. He reported on "Five Year Cures of Carcinoma of the Cervix Uteri" and "Late Complications in Irradiation Treatment of Carcinoma of the Cervix."

L. Adler performed radical vaginal hysterectomy, and after packing away the ureters, placed radium in the parametrial areas for from six to eight hours. In questionable cases he used cross-fire radium therapy, placing the radium source in the rectum and in the vagina, and followed with roentgen radiation. The author also was credited by the Bureau of Investigation, American Medical Association, with "The Adler Treatment, Another Flier in the Cancer-Cure Field."

B. Solomons approved posterior division of the cervix for dysmenorrhea or cervical stenosis. He reports a carcinoma occurring in the cervix that had a posterior division. Treatment was by Wertheim procedure.

Henry Schmitz pioneered the use of radium and x-ray in the treatment of carcinoma of the cervix. His clinical grouping of the extent of the disease is still favored in many centers. His microscopic grading of cervical cancer was among the earliest attempts in this regard. His belief that chronic irritation of the cervix predisposed to the formation of invasive carcinoma stimulated his meticulous study of removed cervices, in which he found early invasive cancer not suspected on clinical examination. He pioneered so-called "supervoltage" x-ray therapy, describing the biologic effect and physical principles. As one author concludes, "His work in the physics of radiation (he standardized dosage) made possible the use of these agents in the treatment of carcinoma of the cervix."

L. Calkins, in a careful follow-up of 500 consecutive patients with carcinoma of the cervix, reported on survival in the primary cases and re-treatment of the persistent or recurrent cases. His demonstration of the value of re-treatment has been an important contribution to the case of the "hopeless" stage of the disease.

T. B. Sellers, writing on the use of radium in the treatment of benign and malignant conditions, advised every gynecologist to familiarize himself with the therapeutic properties of this agent. He says that much of the prejudice against the use of radium is due to three things: (1) faulty technique in its application; (2) improper dosage; (3) a lack of knowledge of its indications and its limitations. He reported three instances of carcinoma of the cervix in 1,390 obstetrical patients. His most recent investigation has been to determine the cause of death in carcinoma of the cervix and the means of extending the patient's life by the relief of urinary tract obstruction.

F. H. Falls stressed early diagnosis by regular examination of persons with a constitutional tendency. He believed the Schiller and Clark tests to be important procedures. He admonished: "Biopsy all suspicious cases." Later, he discussed malignant changes in fibroid uteri, which he stated were not rare in combination. He stressed procedures to rule malignant disease in or out.

J. C. King reported his end results in cases of carcinoma of the cervix treated by radiation therapy, which procedure he favored. He advised fractional therapy and studied the effect on the tumor by weekly biopsy specimens.

H. S. Everett studied and described the secondary effects of both cancer and irradiation treatment on the bladder and ureters. His studies demonstrated the importance of investigating the urinary tract before and after treatment. He found that variation in the amount of radium irradiation administered and, more especially, in the time required to administer it was of more importance than variation in the x-ray therapy, provided excessive x-ray dosage was avoided.

W. R. Cooke believes that since 1925 early diagnosis has been the responsibility of the physician. Diagnosis should be made by biopsy and treatment should be by x-ray and radium.

B. C. Hirst stated that cancer of the cervix complicating pregnancy was more common in Europe and suggested better prenatal observation in the United States. He believed inspection of the cervix to be advisable twice during pregnancy and for symptoms of threatened abortion of over two weeks' duration. In a long-range plan for detection of early cancer, he found one malignant lesion by 222 cervical smears. Later, in reporting on 3,674 pregnant women studied by smears and sponge biopsies, he reported three instances of complicating carcinoma. X-ray and radium used in minimal carcinoma in early pregnancy gave comparable results to its use in the nonpregnant patient, but he observed that there was a tendency toward radical surgery.

R. S. Cron found that deep x-ray had replaced surgery in the treatment of advanced carcinoma. He favored radium and x-ray in all cervical cancer. "We need," he stated, "more experience on the combined use of x-ray, radium

and surgery.'' Twenty-four years later he stated, ''There are so few operators capable of performing the radical operation that it is, in the best interest of the patient, not wise.'' Surgery following x-ray and radium has not improved the end results, he concludes.

R. A. Kimbrough grouped 120 cases according to the Schmitz clinical classification and the Martzloff histologic classification. He compared the response of each group and type to irradiation and found the basal cell type to be most responsive. The relation of mode of growth to the end result showed that the papillary type gave the best result and the infiltrating type the poorest result. In the relation of age to the end result, it was shown that the best results were in the age group 50 to 55.

In another study he found that 20 per cent of 87 patients who lived five years following therapy subsequently died of cancer, 4 per cent later succumbed to cancer after surviving ten years, and none of 44, after living thirteen years, had since died of cancer.

From 1913 to 1926, 479 patients with cervical carcinoma were admitted to the University of Pennsylvania gynecology service. These were grouped according to therapy, stage, and histology, and the follow-up was carefully reported. In 1948 he reported a five-year survival of 27.6 per cent (absolute), but a relative five-year salvage of 32.4 per cent.

V. S. Counseller reported on enterovaginal fistula following the application of radium. He reported two instances of two malignant tumors in the same uterus. Although he believed 90 per cent of carcinomas of the fundus are managed adequately by total abdominal hysterectomy alone, he felt that the Wertheim type of hysterectomy may be employed in a few cases of carcinoma of the cervix; these are cases in which the grade of malignancy is low and the patients are in the early stage of the disease.

R. A. Ross and associates carried on extensive evaluation of genital smears in detecting intraepithelial carcinoma of the cervix. It is believed that the diagnosis of this lesion by the smear method necessitates pathological verification. He advocates delegating responsibility for all patients with malignancy to one member of the department.

B. Carter determined the per cent of false negatives in genital smears in the diagnosis of adenocarcinoma of the uterus, and compared them to the false negatives in squamous cell cervical cancer. His method of management of carcinoma in situ of the cervix helped to crystallize thinking in this problem.

Radical panhysterectomy and pelvic lymphadenectomy were carried out in his clinic as the primary therapy and in conjunction with complete or partial radiotherapy. The complications and survivals formed the basis for his evaluation of these procedures. Preoperative irradiation, with added radical operation, seemed to predispose to the occurrence of bladder fistulas. The author called attention to seven patients who had adenocarcinoma of the cervix. Six of these patients had received preoperative irradiation therapy; three of these patients showed node involvement with cancer. He reasons, therefore, that ''radical surgery'' is indicated in those patients who are considered good risks. He also favors the operation in treatment of carcinoma of the cervix complicated by early pregnancy, as in this way valuable loss of time will be prevented.

J. I. Brewer stated that there is no adequate treatment of cervical carcinoma at present; therefore, it is feasible to try surgery again. He cautioned that a general swing toward surgery for carcinoma of the cervix should not be made at this time—not until follow-ups from the large centers have covered ten or fifteen years so that we can have a true evaluation of the use of surgery in the treatment of cancer of the cervix.

G. W. Waterman has used small sources in long radium element needles to treat carcinoma of the cervix—his description of the technique is excellent and

the follow-up of cases treated at the Rhode Island Hospital show a 36.7 per cent relative survival in 522 patients.

W. E. Studdiford described 16 preclinical carcinomas of the cervix found at Bellevue Hospital since 1947 by four quadrant biopsies, and cervical smears with Ayers spatula. Thirteen were intraepithelial, and three were early invasive.

A. W. Diddle followed 152 carcinomas of the cervix which were considered to have had inadequate or improper management prior to their admission to the University of Iowa Hospital. Of 107 observed for a five-year period, only eight were surviving without recurrence. In a later study on five carcinomas of the cervix occurring in women less than 25 years of age, the impression he obtained is that of a grave prognosis in patients with cervical carcinoma occurring before the age of 20. In a five-year survey of patients treated between the years 1936 and 1940, the over-all five-year survival was 33.2 per cent. He condemns the procedure of postirradiation hysterectomy. In a study of anaplastic epithelium it was found by nuclear measurements that the relative nuclear volume curves were similar for anaplastic and carcinomatous epithelium. Both of these differed strikingly from the normal.

F. R. Smith contributed a painstaking study of 3,106 patients admitted to Memorial Hospital with the diagnosis of carcinoma of the cervix, in which he determined the relationship of nationality to carcinoma of the cervix. There was a relatively low Jewish incidence and a relatively high Italian and Scotch-English incidence. The incidence of bladder fistulas in irradiated and non-irradiated patients he found to be twice as high in untreated patients. In attempting to determine the etiology of cervix cancer the author concluded that parturition, financial status, length of time between marriage and first delivery, Lysol douches, more than one instrument delivery, dry labor, and untreated cervical lesions as manifested by leukorrhea are all important factors.

J. P. Greenhill wrote on the value of sympathectomy and intraspinal alcohol injection for relief of pelvic pain.

J. R. Willson reported on three cervical carcinomas complicating pregnancy. He favored irradiation therapy and stressed the importance of early diagnosis.

W. L. Thomas discussed complications of radiation therapy used in the treatment of carcinoma of the cervix. He believed that radiotherapy is regarded universally as a method of choice in spite of these unavoidable complications. Later, in conjunction with Carter and Parker, he reported on their experience with radical panhysterectomy and radical lymphadenectomy. They believed that the operative procedure was safe when carried out under the ideal conditions which they listed. Complications in the form of urinary tract fistulas were frequent in the irradiated group. They demonstrated that regional lymph nodes show definite evidence of x-ray reaction with modern high-voltage techniques and reasoned that cancer cells are destroyed in many instances.

T. L. Montgomery stated that two types of cervical disease concern the obstetrician: inflammatory and precancerous. He stressed the need of restoring the birth canal to natural contour and integument and the importance of operative repair or cautery treatment when indicated during the postnatal period.

W. E. Brown concluded that carcinoma in situ was difficult to diagnose in pregnancy, as many apparently malignant lesions are reversible. When diagnosed he believes that no treatment is necessary during the pregnancy. In the first stages of carcinoma early in pregnancy he believes in radium and x-ray therapy; in late pregnancy, in the Porro procedure followed by x-ray and radium. In an evaluation of x-ray therapy for carcinoma of the cervix, he demonstrated the difficulty of administering adequate dosage to the gland-bearing areas and recommended procedures to assure adequate radiation to these areas. He believes that 5,000 to 6,000 tissue roentgens appear to be the minimal concentration of radiation that will eradicate carcinoma in the pelvic lymph nodes.

A. C. Barnes, using cobalt^{60} in needles, has outlined a technique for uniform distribution of dosage without major "hot spots" using template guides. This method, he believes, permits precision dosage to be individualized, and is apparently well tolerated and without unusual or unsolvable dangers.

W. O. Johnson discussed twelve cases of carcinoma of the cervix associated with pregnancy, an incidence of 0.04 per cent, which represented 1.54 per cent of all cases of carcinoma of the cervix treated in the Louisville General Hospital during a fifteen-year period. He advised that all products of conception should be removed by the abdominal route. He advocated a combination of radium, x-ray, and radical surgery in selected cases.

H. E. Schmitz achieved 42 per cent five-year survival in patients suffering from carcinoma of the cervix and treated by combined radium and high-voltage x-ray. The effect of these agents on the tumor cells was determined by periodic biopsy. He determined that the clinical extent of the disease, not the cell type, influenced the prognosis. He evaluated radical surgical procedures in radioresistant tumors, and various means of diverting the urinary stream in cases where the bladder and rectum had to be sacrificed. Carcinoma in situ diagnosed by smear and confirmed by ring biopsy, was treated conservatively by watchful expectancy in the young; by conservative amputation or cautery in the intermediate group; by total hysterectomy and conservation of the ovary in the menopausal age group. His stand in favor of irradiation as the primary therapy for invasive carcinoma of the cervix has been steadfast. He carried out studies on the control of intractable pain due to advanced carcinoma of the cervix by presacral neurectomy or subarachnoid alcohol injection as reported with Greenhill. Observations on the procedure of pelvic exenteration carried on in his clinic conclude the publications.

W. G. Cosbie described the complications of irradiation treatment of carcinoma of the cervix. His results of treatment in the patients suffering from cancer of the stump have been better than the results of the treatment of the patients with cancer of the cervix when the body of the uterus was present. In studying the fate of the patient with advanced cancer of the cervix he concluded that years of palliation have been gained for many by means of irradiation.

L. M. Randall studied "factitial proctitis" and advised nonoperative treatment. Colostomy, in his opinion, should not be considered as part of the treatment of factitial lesions of the rectum. In a review of the literature from 1919 to 1947 of 15,476 cervical carcinomas, he found that 4.5 per cent were adenocarcinomas. He determined that adenocarcinoma was much more resistant to x-ray and radium than squamous carcinoma. He believed operation, with or without supplemental radiation, to be the treatment of choice for adenocarcinoma of the cervix.

W. M. Long favored the use of radium and x-ray in the treatment of cervical cancer, and stated that although this disease could be treated rationally with radical surgery, the end results have not proved that surgery is superior to radiation treatment. A possible future treatment, he wrote in 1930, will include the use of radium in the vagina and cervix, followed by removal of the glands by surgery, and finally x-ray therapy to the pelvis.

W. F. Mengert reviewed the theories of etiology, history of the surgical attack, and history of radiation therapy of cervix cancer as well as the various views on intraepithelial cancer and concluded with a review of the advances made by exfoliative cytology.

A. B. Hunt found that although the Mayo Clinic population is 7 to 8 per cent Jewish, there were no cases in which the stated preference of the patient's religion was Jewish in 568 cases of cervical cancer observed.

T. Peightal stated that among patients who consulted their physicians within two months after the onset of symptoms, only 36 per cent were diagnosed cor-

rectly. He stressed proper biopsy, use of the colposcope, the vital stain technique of Schiller, and the Papanicolaou staining technique as vital aids in early diagnosis.

J. P. Hennessy could find only 28 cases of coexistent carcinoma and sarcoma of the uterus reported in the literature. He reported an adenocarcinoma and sarcoma in the same uterus and commented on the considerable confusion in terminology.

C. D. Read presented his views in favor of radical surgery for cancer of the cervix. He felt that although the five-year cure rate by radiation was good, there was a very rapid decline in the ten-year salvage. His observations are based on the work of Victor Bonney.

F. R. Lock discovered 165 cervical cancers in 1,797 biopsy specimens studied. Of this series 72.7 per cent had Stage I or II involvement. Twenty-nine carcinomas were discovered which were considered clinically to be benign cervical lesions.

R. R. de Alvarez determined the cause of death in 55 patients who died of cervical carcinoma, proved by autopsy. Urologic causes accounted for 40 per cent, pulmonary 31 per cent, gastrointestinal 13 per cent. He listed the sites of metastases and postulated that nephrostomy, ureterostomy, palliative colostomy, and bowel shunting may be lifesaving and life-prolonging measures.

D. G. Morton, as early as 1924, stated that 90 per cent of cervical cancers are treated best by radium and x-ray. A small proportion of the cases are best treated by Wertheim operation under special conditions and on carefully selected patients. The chief value of this operation, he observed, lies in the permanence of the cure when this is accomplished at all. He believed the most satisfactory indication in the prognosis of cervix cancer to be the clinical extent of the growth at the onset of treatment. Histological type is of no value in prognosis. Later, after a pathological study of a number of uteri removed by radical operation following preliminary radiation by accepted methods, he concluded that recurrence took place in approximately 50 per cent of Group I and II cases (operable cases) treated by radiation and presumed that recurrence is probably due to the persistence of live cancer cells in the cervix in a large proportion of these. He therefore believed that it is premature to discard surgery from consideration in the treatment of truly early cases; employing a combination of irradiation and surgery he obtained 67.8 per cent five-year survival in selected cases. Morton studied the cause of death in treated and untreated patients and reported the variation in spread and distant metastases in both groups. His microscopic studies of cell types and their response to therapy revealed the inaccuracy of attempts to determine therapeutic responses on cellular characteristics alone. His finding of a distinctly lower incidence of glandular involvement in x-radiated patients subjected to surgery suggests that modern roentgen techniques may make lymphadenectomy unnecessary.

So ends the story of the contributions of the Fellows of the American Association to our knowledge of cervix cancer. That these sixty-six years have been fruitful is evident. To have brought in spirit the founders of this Association and their successors to our meeting has been a pleasant privilege which develops an understanding of our rich heritage and an appreciation of the privilege of Fellowship in this organization.

If this review of the efforts of our illustrious predecessors and our worthy contemporaries stimulates our present Fellows to renewed efforts toward solving this perplexing disease which takes mothers in the prime years when their love and counsel is so important to family and husband, then I shall have succeeded in attaining my objective.

In conclusion, I can think of no greater admonition than to quote the essayist, Michael de Montaigne, who wrote:

> Whenever a new discovery is reported to the scientific world, they say first, "It is probably not true." Thereafter, when the truth of the new proposition has been demonstrated beyond question, they say, "Yes, it may be true, but it is not important." Finally, when sufficient time has elapsed to fully evidence its importance, they say, "Yes, surely it is important, but it is no longer new."

I wish to acknowledge the assistance of J. H. Isaacs, M.D., American Cancer Society Fellow, in preparing the bibliography.

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RAISON D'ÊTRE OF A CATHOLIC MEDICAL SCHOOL*

VERY REVEREND JAMES T. HUSSEY, S.J.
PRESIDENT, LOYOLA UNIVERSITY
CHICAGO, ILL.

YOU will understand immediately why I was extremely pleased to accept your President's flattering invitation to address you this evening.

There is nothing more interesting or exciting on this earth than life in its various forms. For most people the birth of a human child has never and will never lose its fascination. Your association deals largely with the myriad problems involved in the mysterious conception and early development of human life. The special dignity of this group arises precisely from the fact that your specialty revolves around the mystery of birth.

Because of your work and the transmission to posterity of your clinical observations, millions of children in generations to come will know healthy life.

No one is more aware than you of the high death rate of both mothers and infants at the turn of the century. No one but your group is more keenly conscious of the present low mortality rate brought about by your scientific research and advancement in knowledge. Because of your interest, your sacrifice of yourself, distress to mothers and families has been removed throughout the world. It is indeed a cherished privilege to be with you on this important occasion.

The fact that Dr. Herbert Schmitz, Chairman of our Department of Obstetrics and Gynecology, is President of your Association makes me particularly proud. We are fully aware of his excellent and sacrificial work for medical education at Loyola University. This extension of honor you have given to him is a source of gratification to us. Not only because it stimulates the members of his department in Chicago to fuller dedication to their academic pursuits, but because it redounds, also, to the prestige of the entire faculty of the Stritch School of Medicine of Loyola University. I know from personal experience that his activities in your Association have brought inspiration not only to the members of his own department but to the other departments of the medical school as well.

In the course of a dinner party last week, I was invited to join a group of gracious people for dinner in Chicago on this very evening. When I explained the reason why I could not attend, I was immediately asked, by a charming woman of many years, what I was going to say to the American Association of Obstetricians and Gynecologists.

The question made it obvious that the inquirer thought I was preparing to read a scientific paper pertinent to your field in medicine. The questioner

*Special Address, delivered at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 10, 1954.

seemed relieved and satisfied when I explained that I was merely proposing to explain briefly the answer to a question which I have been asked many times at the annual meeting of the Association of American Medical Colleges. Why is it that an unendowed university, such as Loyola, has gone, and will continue to go, to so much trouble and expense to keep on with our tradition of offering medical education despite the numerous difficulties the administration of any university faces when it studies its medical school budget?

The basic reason is this. We are primarily interested in man. We are not alone in this but we have a concept of man which is not shared by everyone. It is a concept of man, however, that surrounds him with tremendous dignity. It is a concept which takes into account that which is material and also that which is spiritual.

As you know, for several years I dealt with medical school students as their spiritual counselor. I watched them dissect cadavers in the anatomy laboratory. I observed them performing experiments on animals in the physiology laboratory. I beheld them peering at their test tubes in the biochemistry laboratory. I heard them discuss clinical patients as cases without reference to the fact that the diseased patient was a human being, composed of considerably more than a mysterious conglomeration of cells. I got to understand how, in the early years of medical study at least, a student could easily grow to regard his patient as being nothing more than a form of matter.

Medicine, as it is taught at Loyola University, differs in no substantial way from the medicine that is taught in any other school. We do not have a special type of mathematics and physics in the arts college. We do not have a special type of anatomy and pharmacology in the medical school.

A student from any other school could walk into the classroom, laboratory, clinic, or hospital and find himself at home. The lectures, the textbooks, the techniques would be familiar. He might even be in the school for a relatively long period of time without becoming aware that we had a special reason for engaging in medical education. When he did notice the difference he would discover that it was in an attitude maintained by the administration and the faculty. He would find that there was a belief prevalent that man is composed not only of a body, but of a spiritual soul.

The background for this belief goes briefly as follows. In our concept man is created by God. In his intellect and will, man is created to the image and likeness of God. He possesses an immortal soul which has a divine destiny.

This concept endows the human being with a dignity consonant with his divine origin and his divine destiny. It conceives of man as not only an animal, but as an animal supernaturally raised to the childhood of God.

Independently of other considerations, this basic idea makes as much of man as can be made of man. From the idea comes understanding of the purpose of this life. There comes hope for a better world and permanent happiness even though this happiness be found in another world.

Everyone, even the most uneducated, has a philosophy of life. Each one constructs his own philosophy of life from what he is taught, what he experiences, what he reads, what he hears from others, and from his own reflections. A man's philosophy of life usually takes into account himself, his origin, his purpose in this life, his destiny, and his relationship to society. Obviously, a difference in a man's philosophy of life makes a noteworthy difference in a man's personal conduct and his conduct as a member of society.

Let the human race have its beginning as far back in history as you wish. Then recognize the instinctive urge which man has demonstrated throughout history to perfect himself and to make this a better world in which to live. Now glance across the globe, and observe what man is making of himself and his world.

Does it make any difference whether a man believes in the existence of God and the existence of an immortal soul? Does it make any difference whether man brings God into his life or ignores him? Are there individuals and are there societies who live better, more purposeful, happier, and more hopeful lives because of their belief in the existence of God and the prospect of eternal happiness?

Obviously I believe that it makes a difference. Obviously I believe that man and the world would be better if God were brought more into the home, into society, into government, into our daily living. Obviously I think it makes a difference whether a medical school student is brought up to believe that man is more than a bundle of bones and flesh, as some modern philosophers maintain he is.

Finally, it makes a difference whether man is to be regarded as an isolated individual or as a member of society. It makes a tremendous difference whether or not a medical student is taught that he himself has an extraordinarily important position in society, with clear-cut obligations and responsibilities to society.

I know full well that this subject is not ignored in other schools. I merely wish to say that it is strongly emphasized at Loyola.

Because of the limitation of time, I am going to make a sharp turn to the right at this point. I am going to abandon the general discussion of an interest in teaching medical school students their relationships to society and focus attention on a few of the specific relationships to society which we expect our graduates to recognize throughout their practice. The only reason the curve seems to be sharp and sudden is that it is.

Until our generation, the social role of the physician was relatively limited. He carried on his practice, for the most part, alone. Your society was founded, as you well know, in 1888. It is one of the older groups in American medicine. What was the function of the medical society in 1900? For the most part, it provided apt means for the exchange of scientific data, for relaxation with one's own kind, and for peaceful collaboration with friendly colleagues. You know that even these associations were limited. In those days how many medical meetings did a physician have to attend in

the course of a month, a year? How many maintained, in addition to a busy practice, a faculty chairmanship? How many actively participated in city, state, and national groups? In addition to all this, how many had three or four demanding hospital assignments?

There was a time when the practice of medicine was a simple thing. I will pass over the question of whether medicine today is or is not overorganized. I have a strong conviction that it is. I know too many doctors not to realize the enormous demands made upon their time by participation in a variety of groups related to medicine.

This is an aside which is not meant to be idle flattery: but since wives and families are present, I say that more than ever saintly virtues are demanded of a doctor's wife today.

Incidentally and parenthetically, I might add that many activities are overorganized in our times. University education has not escaped the blight. It is no longer a question of conducting a university and even conducting it well. One must keep peace separately with associations and agencies connected with every school and department of the university.

There was a time when the president of a university could provide a budget for the librarian and indicate a course to follow. Now the librarian tells the president how many librarians and books the accreditating agencies expect. It is not enough that the university as a whole is accredited by an appropriate agency; each school has to have its own accrediting. In some instances separate departments within a school must win the approval of an outside independent society. I know what it means to be overorganized. But that is not the point of my remarks tonight.

The distinctive element of medical associations today is their changed relationship to society as a whole. Once you functioned separate and apart. Now your deliberations, your very mode of exercising your profession are considered to be the legitimate concern of labor unions, legislators, news columnists, novelists, and repeated government surveys. Too many laymen are expounding the manner in which medicine should be practiced.

I wish I could say that the medical profession was absolutely blameless in all this. Dr. Herbert Schmitz, your President, knows that I have a long-enduring interest and sympathy with the profession.

I can remember the time when the doctor enjoyed the trust and respect not only of his patients but of the community. I have referred to the fact that today your profession is the subject of open discussion. There has been talk of how the government will regulate your practice.

What I would like to say to you tonight is that it is not enough for any medical society to react to the public and the press with irritation and disdain. Nor is it quite enough in my opinion to leave these matters to a small group of officers of the A. M. A.

Much of modern life is under hard public scrutiny and re-evaluation. At the present moment medicine is in the spotlight of that cold scrutiny. Lay journals are full of articles on medicine and medical practice.

There is admittedly a tendency for groups such as yours to stand apart from social and political controversies. Good can come from this. But today, even though science gains by this abstention, it can have disastrous effects upon your profession.

I repeat, today, your profession is being attacked on all sides. It has already lost a considerable amount of prestige that it formerly enjoyed. One reason is that there is much talk about split fees and unnecessary surgery and the like.

In every profession there are excellent men and poor men. You know, as well as I do, that not every minister of religion is a saint. You have experienced, as have I, the far-reaching damage that has been caused by the unsaintly. There is some tendency in human nature, the psychological causes of which we shall not examine, which influences most people to search out for the flaws in an individual and in groups, and make much of the flaws which are always there. The tendency ignores the vast amount of good in every individual and in most groups to the extent that the whole picture is distorted, unreal, and unfair.

Certainly it is unfair to the excellent people who comprise worthy associations such as your own. Because one physician is careless in his diagnosis, more careless in his treatment, unwilling to help the needy, influenced in his practice by his patients' wealth, why should ten reputable, charitable, devoted, competent, painstaking physicians suffer? Without exploring the reasons, I recognize the regrettable fact. The conduct of a minority in a profession can bring the scrutiny of the public, the press, the government to bear on the entire profession. I think it unfortunate, but true, that too many of the problems of medicine in the social sphere are in danger of being left to those who have more goodwill than insight. I wish there were an effective method of stimulating medical men of your capacity to closer participation in the daily stresses and demands put forward for the regulation of your profession. I understand fully how busy you are, how preoccupied with the internal problems of your profession. But think of how many selfish people there are. How many people there are eager to get whatever they can for nothing, ungrateful when they get it. Think of how many (there are some) disgruntled doctors there are.

I wonder whether this Association is kept abreast of the legislation proposed in the various state capitals and in Washington. I wonder whether this Association knows, checks, and approves the experts who are their spokesmen and upon whom they rely in these matters of legislation. I wonder to what degree the official position of medicine represents the views of practitioners in your locality. These things should be known and evaluated. Doctors should solve sociomedical problems, not politicians.

When proposals for hospital accreditation and control are put into effect, I would feel more secure if I were certain that these proposals had enjoyed a study and the blessing of a committee of this Association. When proposals are made for changes in medical education, and enforced upon schools, I am

sometimes given to wonder what groups of physicians were consulted. I know that there is the constant possibility that new programs in medical education may fall into the hands of a few interested men.

I will ask a question which I cannot answer. Are the brightest and best-trained medical minds always aware of developments made in medical education, and in hospital control?

Unless I am mistaken, too many medical groups hold themselves aloof or semi-aloof from the main stream of social changes. If I knew that this group did, I would ask that this group restudy the question of whether it is any longer possible for so distinguished a body to hold itself even semi-aloof from the whirlpool of problems which involve medicine in the United States today, and not leave these problems to assistants. If only the practice of medicine were less complicated, if the demands from all sides were less numerous, if research and teaching could only go on without stress and strain from outside, the excellent minds in medicine would have time and energy to solve the social problems with which it is presently confronted.

I hope for a simpler way of life for all of us and for your profession in particular.

SOME PROBLEMS OF CURRENT INTEREST RELATING TO CLASSIFICATION AND TREATMENT OF UTERINE CARCINOMA*

JAMES HEYMAN, M.D., STOCKHOLM, SWEDEN

(From the Department of Gynecology, the Radiumhemmet. Chief: H. L. Kottmeier, M.D.)

ON THE basis of experience from thirty-four years of activity in the gynecological department of the Radiumhemmet in Stockholm, 1914 to 1947, and as Editor of the hitherto issued nine volumes of the *Annual Report on the Results of Treatment in Carcinoma of the Uterus,* I wish to discuss some current problems relating to classification and treatment of uterine carcinoma.

The value of different methods of treatment can be estimated only by comparing results presented in uniform and comparable therapeutic statistics.

Uniformity in statistics on carcinoma of the uterus requires precise definitions of the varieties of the disease. The classification system at present used by the collaborators in the *Annual Report*[1] includes—besides the two conventional groups: carcinoma of the cervix and carcinoma of the corpus—four additional groups intended for cases in which the origin of the growth cannot be accurately ascertained. The four groups are called: carcinoma vaginae et cervicis, carcinoma corporis et endocervicis, carcinoma uteri et ovarii, and carcinoma pelvis. The system permits each case of primary carcinoma of the uterus to be exactly and uniformly classified. It has been used in the Radiumhemmet since 1934.

Comparability of results requires that the figures to be compared relate to material of equal clinical quality in respect to curability. The statements presented in the *Annual Report* confirm the fact that great variations in quality occur at different institutions. In order to obtain comparability it is necessary to divide the total material into groups or stages containing cases of equal anatomical spread. Staging and the comparing of stage rates are for the time being the only means by which comparability can be secured.

At the Seventh International Congress of Radiology in Copenhagen, 1953, a number of important decisions were made concerning staging. Among other things it was recommended that two types of staging should be used, clinical staging based on clinical examination including biopsy, and surgical staging based, in addition, on findings at operation and microscopic examination of the removed specimen. The former should be used when comparing results obtained by different methods of treatment, the latter only when comparing surgical results. It is not justifiable to compare statistics based on surgically classified cases with those based on clinically classified cases.

*The Joseph Price Oration, presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

Staging as a means of securing comparable material has been much criticized. Heyman, Kottmeier, and Segerdahl[12] have investigated the reliability of clinical staging. Each of 161 cases of cervical carcinoma was examined by two examiners. Differences in staging occurred in 18 cases, i.e., in 11.2 per cent. A statistical analysis of the influence of the differences in staging on the presumptive five-year recovery rate shows that in Stage I the rate will differ by only 1 per cent and in Stage II by 0.2 per cent. Because of its importance, stage grouping should never be left to a young assistant but should be carried out by one or two experienced gynecologists, preferably permanent members of the staff.

Carcinoma of the Cervix

Classification.—

At present there are only a few important problems concerning classification in carcinoma of the cervix where agreement has not been reached. The clinical staging used in the *Annual Report* seems to be almost universally accepted. A few minor alterations of the definitions of the four stages of invasive carcinoma are suggested in Volume 9.

As to Stage 0, i.e., the case of carcinoma of the cervix in its subclinical stage, it is highly desirable to reach agreement on a precise definition. Further investigations are required for solving this problem. With a view to comparability of the statistics it is important that the cases of noninvasive carcinoma and those of invasive carcinoma should be reported separately.

In the *Annual Report,*[1] 22 of 72 collaborators have furnished information on 246 cases allotted to Stage 0 in 1947 and previous years, i.e., 2.9 per cent of the total number of cervical cases examined. Three collaborators (Koller in Basel, Held in Zurich, and Brack in Baltimore) report on 177 cases allotted to Stage 0, i.e., 12.7 per cent of the total number of cervical cases treated during the same period at their institutions. The furnished material on Stage 0 cases is still too small for statistical analysis.

Treatment.—

Intracavitary radium application is for the time being our most effective weapon in the control of cervical carcinoma. Details concerning the application technique are of secondary importance. Good results can be obtained by various technical procedures. It is obvious that adequate radiotherapy requires experience of the technique used, of the immediate and late injuries that may follow, and a careful individualization of the treatment with a view to the macroscopic appearance and extension of the growth and to the general condition of the patient. For these reasons radiotherapy should be centralized at institutions with a sufficient number of beds, with all technical facilities available, and conducted by experienced specialists.

The results obtained at the Radiumhemmet in 1936 through 1948 have been collated by Kottmeier (Tables I, II, and III).

The statistics relate to unselected material since the Radiumhemmet is responsible for the treatment of all cases of cervical carcinoma that occur within a defined geographical area. During the period 1936 through 1948, odd cases

only have been primarily operated upon in Sweden. Needless to say the statistics are compiled in accordance with the rules laid down in the *Annual Report.* The Stockholm method of intracavitary radium treatment has been recently described in detail by Kottmeier.[14] Surgery is used in cases of failure or of local recurrence following radiotherapy.

TABLE I. FIVE-YEAR RECOVERY RATES IN CASES* OF CARCINOMA OF THE CERVIX TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

Total number of cases examined	3,858
Alive with no evidence of the disease	1,564
Absolute recovery rate	40.5%
Total number of cases treated	3,704
Alive with no evidence of the disease	1,564
Relative recovery rate	42.2%

*All cases microscopically verified; 100% follow-up. Stage 0 cases excluded.

TABLE II. DISTRIBUTION BY STAGES OF CASES OF CARCINOMA OF THE CERVIX TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

Stage I	452 cases	(12.2%)
Stage II	1,904 cases	(51.4%)
Stage III	1,040 cases	(28.1%)
Stage IV	308 cases	(8.3%)
Total	3,704 cases	

TABLE III. FIVE-YEAR RECOVERY RATE IN THE VARIOUS STAGES OF CASES OF CARCINOMA OF THE CERVIX TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

	NO. OF CASES TREATED	ALIVE WITH NO EVIDENCE OF THE DISEASE	RECOVERY RATE
Stage I	452	321	71.0%
Stage II	1,904	958	50.3%
Stage III	1,040	257	24.7%
Stage IV	308	28	9.1%

Special attention is nowadays paid to the tendency toward substituting surgery for radiotherapy in apparently early, operable cases of carcinoma of the cervix as inaugurated by Meigs.[15] It is hoped that by the extended use of primary surgery it will be possible to cure the "radioresistant" cases and cases with pelvic node metastases, in both of which categories it is generally considered that radiotherapy will fail.

Since they cannot be recognized prior to treatment, it is impracticable to refer only these two types of cases to surgery. It is also impracticable to produce two series of such cases for comparative purposes, one treated by surgery and another by radiotherapy.

The only way at present available for a correct evaluation of the extended use of surgery is as follows:

1. Classify all cases examined at the institution, on the basis of findings at clinical examination prior to any treatment.
2. Let the cases remain in that stage irrespective of any findings at operation or microscopic examination of removed specimens.
3. Report on all cases allotted to Stage I.

4. Compare the results obtained in all Stage I cases between institutions favoring surgery and those favoring radiotherapy.

The statements published in Volume 9 of the *Annual Report*[1] offer a possibility for such evaluation. The submitted figures indicate that the five-year recovery rate in Stage I is 62.5 per cent at institutions in favor of primary surgery and 65.3 per cent at those favoring primary radiotherapy.

Meigs has shown that excellent results can be obtained by the expert surgeon in a series of carefully selected cases. This, however, does not prove that primary surgery is superior to primary radiotherapy. Whereas the value of radiotherapy is ascertained by statistically proved facts, conclusive evidence of the value of primary surgery is not yet available. It seems desirable that the responsibility for the establishment of such evidence should be left to the most expert gynecological surgeons. In the meantime, the extended use of primary surgery should not be advocated. If practiced by the average surgeon and gynecologist the final result may prove catastrophic.

In addition, the advocating of surgery may unnecessarily delay the urgently needed establishment of adequate radiotherapeutic facilities in areas where they are still lacking.

In both the surgical and the radiotherapeutic series, there are a certain number of failures in apparently early cases. I believe that failure in these cases is due to pronounced malignancy, that the cases are identical in both series, and that they are not only "radioresistant" but incurable whether treated by surgery or radiotherapy.

For the reasons mentioned, it seems reasonable to state that there is no urgent need for primary surgery in cervical carcinoma in places where adequate radiotherapy is available.

Carcinoma of the Corpus

Classification.—

For twenty-five years we have at the Radiumhemmet devoted much interest to classification and treatment of carcinoma of the corpus uteri.

In passing, I wish to mention the desirability of dropping the terms carcinoma of the fundus and carcinoma of the endometrium, neither of the terms being adequate and both causing confusion.

In a series of papers, dating from 1934, I have reported on the method of treatment and the classification which we have adopted at the Radiumhemmet in carcinoma of the corpus, and on the results obtained. Since we are to some extent responsible for the problems at present discussed I may be justified in touching upon these problems and answering the criticism to which we have been subjected.

Our method of treatment, the so-called packing method, was gradually developed from 1929 to 1934. A preliminary report appeared in 1936[6] and detailed descriptions in 1941[10] and 1946.[11] The method consists of intracavitary radium treatment combined with hysterectomy in case of failure. Radium containers of equal size, shape, and content are inserted in the uterine cavity sufficient in number to fill the cavity entirely. In addition, radium is applied to

the vagina and in some cases external roentgen irradiation is administered. The containers are inserted in filter capsules, the size of which varies according to the width of the uterine cavity. The same physical dose is given in each case irrespective of the number of irradiators inserted and the size of the filter used. Radiotherapeutic failure is indicated by persistence or reappearance of bleeding or discharge or by increase in size of the uterus. In about 60 per cent of the cases where radiotherapy fails, the signs of failure appear one to four years after radiological treatment.

In order to ensure a reliable comparison between the results obtained by the packing method and our previous results we considered it advisable to improve the classification system previously used. In 1934[5] and in 1936,[6] I drew attention to the cases of uterine carcinoma in which it is impossible to ascertain the origin of the growth, i.e., cases in which there is involvement of both the cervix and the corpus, or of the uterus and the ovary, or of most pelvic organs. A complete system for classification of the various types of primary carcinoma of the uterus was suggested in 1941.[10] It includes the three additional groups previously mentioned and a recommendation to use a fractional curettage in all cases of carcinoma involving the endometrium. The system was published in the first volume (Vol. 5) of the *Annual Report* issued after the war; it was discussed at the International and Fourth American Congress on Obstetrics and Gynecology in New York, 1950, and has since been used by the collaborators in the *Annual Report.*

In my statistics on carcinoma of the corpus I have used the mentioned classification. Eymer[4] criticizes the procedure by stating: "Heyman's statistics are of reduced value because they are based on highly selected material." I am sorry to say that Eymer's statement may easily be misinterpreted. Of course, a comparison of my statistics and those based on cases not similarly classified is not justified. My statistics, however, are based on cases carefully and uniformly classified, which should not be confused with highly selected material.

For clinical staging in carcinoma of the corpus two stages only are convenient: Stage I to include cases in which the growth is confined to the uterus, and Stage II to include cases in which the growth has spread outside the uterus. In addition, it is suggested that cases allotted to Stage I should be subdivided into two groups: Group 1 to include cases in which operation is considered advisable and Group 2 to include the so-called technically operable cases, i.e., cases where the anatomical spread does not hinder a radical removal but which cannot suitably be submitted to hysterectomy because of some serious complicating disease or factor.

The subdividing of Stage I was recommended with a view to securing comparability of operative and radiotherapeutic statistics at a time when the facilities of modern surgery were generally not available. It has the inherent disadvantage that opinions vary greatly at different institutions as to which cases are considered technically though not clinically operable.

Bastiaanse draws attention to this fact. In a paper read before the Thirteenth British Congress of Obstetrics and Gynaecology, Bastiaanse[3] states

that "the clinically inoperable group, which is so prominent in many statistics (Heyman et al., 1941), is almost nonexistent." Although, in his statement to Volume 9 of the *Annual Report,* 19.1 per cent of the total number of corpus cases are allotted to Group 2, all Stage I cases, except one, have been submitted to hysterectomy, according to the previously quoted paper.[3] Both statements relate to cases treated in 1939 through 1946 whereas the quoted Radiumhemmet statistics relate to cases treated in 1914 through 1934.

It should be noted that the Radiumhemmet is a central institution responsible for all cases within its area of activity which need radiological treatment. To institutions similarly organized will be referred all cases unsuitable for surgery, whereas the clinically operable cases will be distributed to a number of gynecological, surgical, and radiotherapeutic institutions. At the Radiumhemmet, 1,239 cases of corpus carcinoma and carcinoma corporis et endocervicis were radiologically treated in 1936 through 1948; simultaneously at least 655 cases were submitted to hysterectomy at various other institutions, within the Radiumhemmet's area of activity.[13] In areas where radiotherapy is differently organized, both the operable and the inoperable cases will be distributed among various institutions, any one of which may see only odd technically operable cases. Thus, differences in the proportion of technically operable cases may be related to differences in the organization of reporting institutions. Until further experience on this point is available, it may be advisable to maintain the present subdivision of Stage I in spite of its inherent defects and the facilities of modern surgery.

In 1936 I[6] discussed the procedure to be adopted in the debatable cases which the pathologist considers most likely to be of carcinomatous nature, though it is impossible to arrive at a definite microscopic diagnosis. It was recommended that such cases should be placed in a separate group. Following this recommendation the proportion of debatable cases was mentioned in my statistics.[7, 9, 10,11]

Tailhefer,[16] in a paper read before the French Academie de Chirurgie in 1952, has criticized my work on corpus carcinoma. The criticism is apparently based entirely on the chapter, "Radiotherapy in Gynecology" of *Modern Trends in Obstetrics and Gynecology* published in 1950.[9] Tailhefer questions whether serious injuries are never caused by our method of treatment, and states that I have entirely omitted to give the relevant information. An answer to the question, however, will be found in several of my papers.[8, 10, 11] Tailhefer considers my work open to even more serious criticism: I have included in my series of treated cases a number of microscopically debatable cases. The figure indicating the proportion of debatable cases is actually given in the article quoted by Tailhefer. Using this figure he recalculates the stated recovery rate, reducing it from 61.4 to 58 per cent. A correct recalculation would result in 59.6 per cent.

Collaborators in the *Annual Report* are requested to allot microscopically debatable cases to Stage 0. In Volume 9 information is submitted on 58 treated cases of which 5 (8.6 per cent) have developed invasive carcinoma.

Treatment.—

As to treatment in carcinoma of the corpus one has at present the choice between three methods: (1) hysterectomy followed by post-operative irradiation, (2) preoperative intracavitary radium treatment followed by hysterectomy, and (3) primary intracavitary radium treatment followed by hysterectomy in case of failure.

The results obtained by any of these methods may be shown by the following five-year recovery rates: (1) 73.5 per cent in a series of 211 cases referred to the Radiumhemmet for postoperative irradiation (1936 through 1948), (2) 70 per cent in a series of 60 operable cases treated by Arneson[2] (1930 through 1947) by intracavitary radium and subsequent hysterectomy, and (3) 65.5 per cent in a series of 1,017 operable cases of carcinoma of the corpus and carcinoma corporis et endocervicis (1936 through 1948) primarily submitted to radiotherapy at the Radiumhemmet—66.8 per cent if cases of carcinoma of the corpus only are considered.

The figures seem to indicate that hysterectomy followed by postoperative radium irradiation is superior to the other two methods. It should, however, be noticed that there are a number of factors influencing the comparability of the statistics. First, Arneson's results relate to a small series of cases, and variations due to chance cannot be excluded. Further, in the last series the cases are clinically classified; thus, the series most likely includes a number of cases which at operation would be classified as Stage II and, in addition, a number of technically operable cases. Both these categories are excluded from the first series and so are the cases in which a radical operation could not be carried out and those that died following operation. For the reasons mentioned it seems reasonable to assume that equally good results can be obtained with each of the three methods.

I have never claimed that primary radiotherapy in the treatment of operable cases of carcinoma of the corpus is superior to the other methods mentioned. I cannot agree, however, with those who claim that hysterectomy is the method of choice in these cases. Primary radiotherapy is an equally justifiable method at institutions where the necessary technical facilities are available, where the treatment is handled by gynecologists satisfactorily experienced in radiotherapy, and which have at their disposal an efficiently functioning follow-up department.

Further experience is required before we can tell if any one of the methods mentioned is superior to the other. Until sufficient experience has been obtained and until a decision based on statistically significant figures can be made, I consider it advisable that each leading institution should maintain and develop the treatment method which that institution considers to be the best.

In conclusion I should like to present the latest statistics on the results obtained at the Radiumhemmet in the treatment of corpus carcinoma (Tables IV, V, VI, and VII). They are quoted from Kottmeier.[13]

TABLE IV. FIVE-YEAR RECOVERY RATES IN CASES* OF CARCINOMA OF THE UTERINE CORPUS TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

Total number of cases examined	1,057
Alive with no evidence of the disease	638
Absolute recovery rate	60.4%
Total number of cases treated	1,032
Alive with no evidence of the disease	638
Relative recovery rate	61.8%

*Stage 0 cases excluded.

TABLE V. FIVE-YEAR RECOVERY RATE IN THE VARIOUS STAGES OF CARCINOMA OF THE CORPUS TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

	NO. OF CASES TREATED	ALIVE WITH NO EVIDENCE OF THE DISEASE	RECOVERY RATE
Stage I	919	614	66.8%
Stage II	113	24	21.2%

TABLE VI. FIVE-YEAR RECOVERY RATES IN CASES OF CARCINOMA CORPORIS ET ENDOCERVICIS TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

Total number of cases examined	235
Alive with no evidence of the disease	68
Absolute recovery rate	28.9%
Total number of cases treated	207
Alive with no evidence of the disease	68
Relative recovery rate	32.9%

TABLE VII. FIVE-YEAR RECOVERY RATE IN OPERABLE AND IN INOPERABLE CASES OF CARCINOMA CORPORIS ET ENDOCERVICIS TREATED AT THE RADIUMHEMMET IN 1936 THROUGH 1948

	NO. OF CASES TREATED	ALIVE WITH NO EVIDENCE OF THE DISEASE	RECOVERY RATE
Operable cases	99	48	48.5%
Inoperable cases	108	20	18.5%

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NITROGEN MUSTARD AND X-RAY IN THE TREATMENT OF PULMONARY METASTASES FROM CHORIOCARCINOMA*

CLAYTON T. BEECHAM, M.D., AUGUSTIN R. PEALE, M.D., AND ROBERT ROBBINS, M.D., PHILADELHIA, PA.

(From the Departments of Obstetrics and Gynecology, Pathology, and Radiology, Temple University Hospital and Medical School)

THE clinical pessimism surrounding choriocarcinoma seems warranted by its unpredictable behavior. Further, the statement made by James Ewing[3] in 1940, "I have been unable to find any record of operative cure of choriocarcinoma," finds much support among later students of this entity. The continued work of the Chorionepithelioma Registry of this Association will undoubtedly result in further definitive reports such as Dr. Novak read at the Annual Meeting of the American Association last year. Certainly that paper by Novak and Seah[11] should end some points of confusion.

The uncertainty regarding choriocarcinoma is well shown in discussions of the pulmonary metastases. For instance, many books and papers have stated that metastases, particularly in the lungs, may disappear spontaneously. In fact, such disappearance is said to occur with or without definitive treatment. Park and Lees[12] write that they doubt whether there are more than 20 cases recorded of spontaneous regression in the lung and, further, that there are too many factors involved for these cases to be taken seriously. Supporting Park and Lees is this statement by Holman and Schirmer,[4] "It has been stated that frequently metastases would disappear spontaneously after the parent tumor was removed. We found no evidence to support this in our study and do not believe it."

The treatment used for pulmonary metastases, aside from a complete removal of the uterus and probably the adnexa, has been lobectomy for solitary nodules[8] and x-ray therapy to the lung fields. The results are equivocal. No apparent improvement in the patient's condition was obtained in the cases of McCormick,[9] Wilson,[13] or Dilworth and associates.[2] Mohler and McConnell[10] used testosterone and x-ray without effect.

On the other hand, Lachner and Leventhal,[6] Levi and Haig,[7] Acosta-Sison and Espaniola[1] all report cases in which pulmonary metastases from choriocarcinoma have been cured by x-ray therapy. Acosta-Sison states, "The results of this study point to early hysterectomy and early x-ray of the lung metastases as the surest form of treatment."

Of the 74 authentic cases of choriocarcinoma reported here last year by Novak and Seah, 41 demonstrated pulmonary metastases. When the report was read, 2 of these patients were alive, six months after treatment. One of those living (C.R. No. 220) is a patient of ours.

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

We should like to present studies and therapy employed in this last and in a similar case (C.R. No. 328).

CASE 1.—Mrs. A. M., T. U. H. Tumor Clinic No. 52-2802, Chorionephithelioma Registry No. 220 was aged 22 years, white, para 0. Her last menstrual period was Oct. 14, 1950. Her doctor verified the diagnosis of pregnancy in November, and vaginal bleeding started 9 weeks later (December 17). In Dec. 24, 1950, the uterus was at the level of the umbilicus, gonadotrophins were 12,500 M.U., and the chest x-ray negative. On Jan. 16, 1951, at about the time for the third missed period, a hydatidiform mole was spontaneously passed. The uterus was then curetted. Table I summarizes the findings over the next nine months—Jan. 16, 1951, to Oct. 25, 1951.

It will be noted that a period of seven months had elapsed, during which time the Aschheim-Zondek tests were negative and the patient had three normal periods, the last being on Sept. 2, 1951. The patient presumed she was pregnant and did not consult anyone. On Oct. 25, 1951, three weeks after her first missed period, she noted slight vaginal bleeding, and the following day started a normal seven-day period. Some time in November she developed slight bleeding. On Jan. 9, 1952, she consulted one of us (C. T. B.) for the first time. Physical examination revealed nothing of note except for a scant, muddy discharge from the cervix. The uterus seemed normal in size and the ovaries were within normal limits.

On admission to Temple University Hospital, the Aschheim-Zondek test on urine was positive in a dilution of 1:250; the blood serum was positive 1:10; and the spinal fluid contained 100 R.U. gonadotrophins per 100 c.c. Chest films made at that time showed numerous metastatic lesions throughout both lung fields. Curettage revealed scanty endometrial fragments accompanied by clotted blood. The tissue fragments presented a secretory pattern. The stroma was pseudodecidual in character, and the glands were dilated, tortuous, and elongated. In one area embedded in the blood clot there were two tiny cohesive islands of 10 to 20 cells showing moderate pleomorphism and hyperchromatism. These cells were large and polyhedral. They possessed abundant pale pink cytoplasm and large, irregular nuclei. The nuclear markings, except for hyperchromatism, were pale and vesicular. Prominent single red-staining nucleoli were identified. There was no suggestion of chorionic villus formation. These cells had a decidual or trophoblastic cytoarchitecture, yet on the basis of such scanty material one could only make a description of this disquieting tissue (Fig. 1).

TABLE I. SUMMARY OF SIGNIFICANT OBSERVATIONS OVER A NINE MONTHS' PERIOD IN A CASE OF CHORIOCARCINOMA

1951	VAGINAL BLEEDING	GONADOTROPHINS	CURETTAGE
Jan. 16	Yes	12,500 M.U.	Blood clot only
Feb. 6	Yes	3,000 M.U.	Blood clot
Feb. 23	Yes	--	Blood clot
March 1	Yes	330 M.U.	Hyaline fragments, syncytial cells
March 29	Slight	330 M.U.	Proliferative
May 1	Slight	--	Nonsecretory
May 23	Slight	A-Z negative	None
July 6	Period	A-Z negative	None
Aug. 4	Period	A-Z negative	None
Sept. 2	Period	A-Z negative	None

On Jan. 18, 1952, a panhysterectomy and bilateral salpingo-oophorectomy were performed.

Pathological Findings.—The surgically removed specimen consisted of a uterus complete with cervix, Fallopian tubes, and ovaries. In the opened state the uterus measured 8 by 11 by 5 cm. The endometrial cavity appeared to be normal in size and contour, with a smooth surface. Occupying the myometrium of the anterior wall of the corpus there was a bulging hemorrhagic mass measuring 4 cm. in thickness. This mass had a spongy texture and was readily friable. Each ovary measured 5 by 3 by 2 cm.; and on cut sections disclosed multiple thin-walled cysts filled with clear fluid, averaging 1 cm. in diameter.

Sections taken through the myometrial mass for microscopic study revealed large areas of necrotic material with hemorrhage and tumor tissue. The latter consisted of columns or clusters of trophoblastic cells of both syncytial and Langhans types, which penetrated the

Fig. 1.

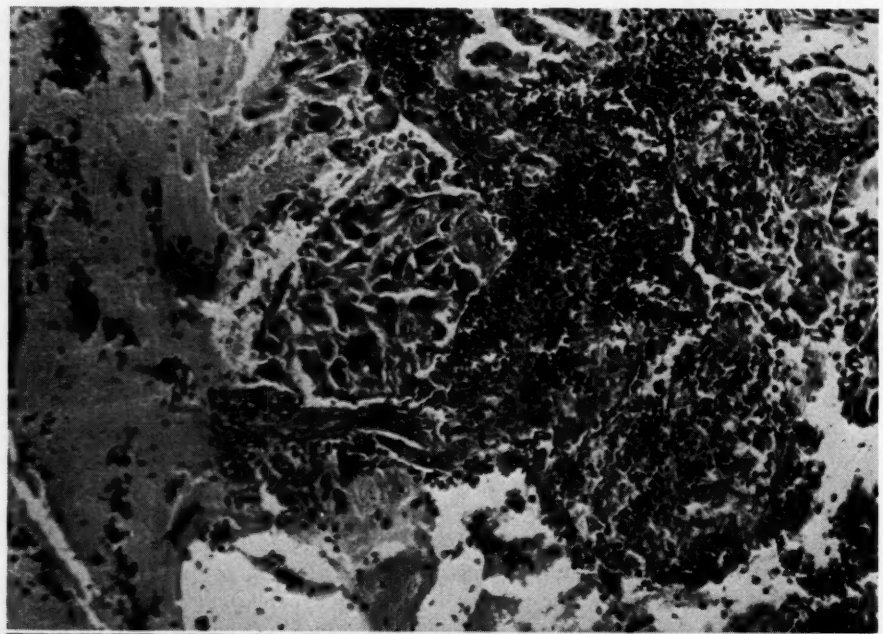

Fig. 2.

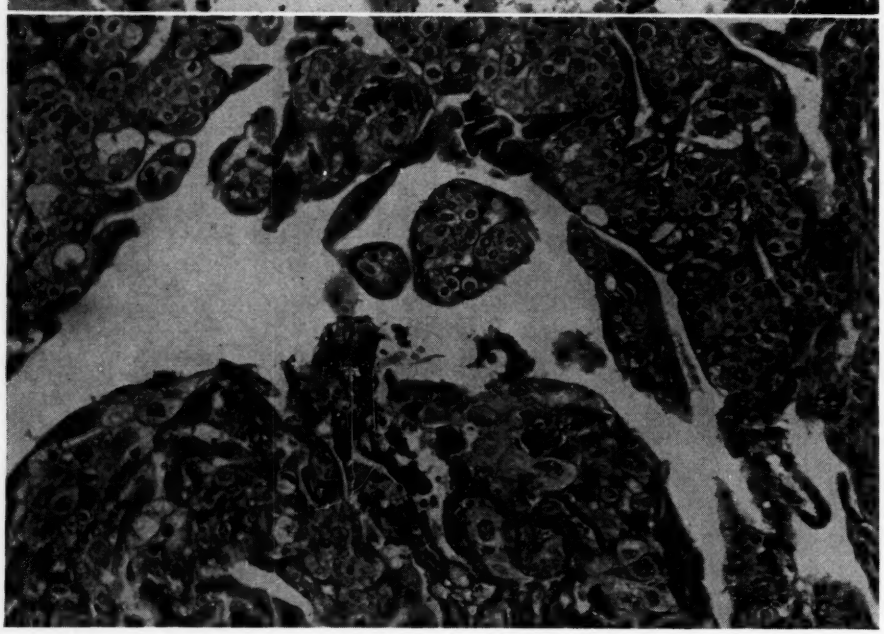

Fig. 1.—Curettage of January, 1952, showing the two tiny islands of decidual or trophoblastic cells. (×200; reduced ¼.)

Fig. 2.—Section taken through the viable tumor area. The neoplastic trophoblastic cells of both syncytial and Langhans types are clearly seen. There is no necrosis or hemorrhage in this field. (×200; reduced ¼.)

muscle wall and appeared within the lumina of the uterine sinuses. The involved muscle tissue revealed degeneration and necrosis (Fig. 2). The endometrium presented a secretory pattern; its stroma was pseudodecidual. The ovaries contained multiple cystic follicles, a few of which disclosed luteinization.

Fig. 3. Fig. 4.

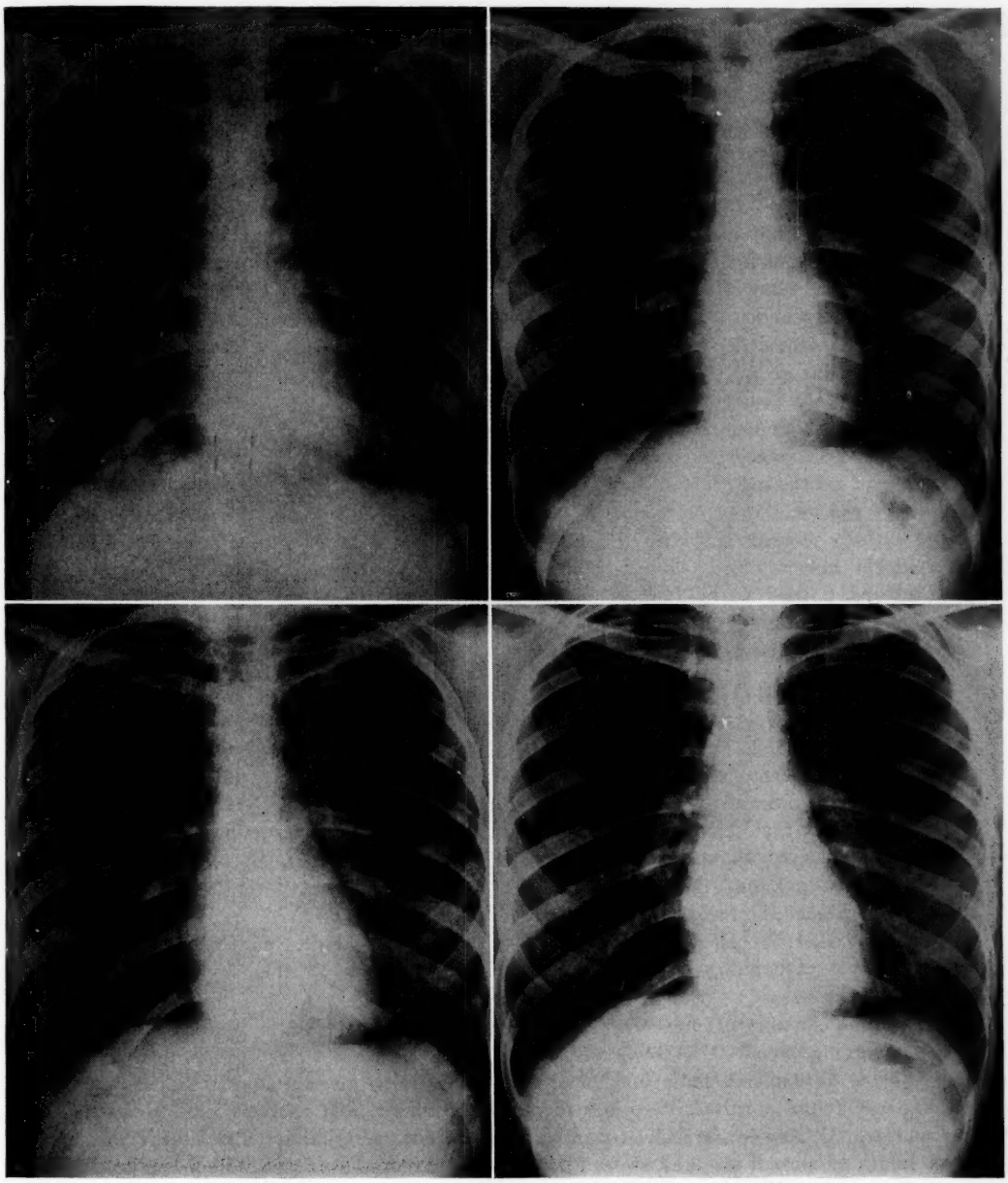

Fig. 5. Fig. 6.

Fig. 3.—Chest film made four weeks after operation showing increase in size and number of metastases.

Fig. 4.—Chest film made on April 7, 1952, twelve weeks after operation and three weeks following completion of irradiation and mustard.

Fig. 5.—Chest film made on May 28, 1952, showing disappearance of most of the metastatic nodules.

Fig. 6.—Chest film taken June 17, 1953, showing the clear lung fields as they remain today.

The pathological diagnoses were choriocarcinoma of the uterus, low-grade chronic cervicitis, and multiple follicular and lutein cysts of the ovaries.

Twelve days following operation the patient was in very poor condition. She had lost weight from 109 to 94 pounds and had an almost constant cough which was productive of increasing amounts of blood. Testosterone, 100 mg. per day, was started at this point. Four weeks postoperatively the patient had difficulty in getting around, because of extreme weakness. At this point she had received 1,400 mg. of testosterone. The A-Z test was positive in dilution of 1:500 on urine and on serum 1:1,000. At this time the chest films showed a striking increase in the size and number of metastases (Fig. 3). Because of this and the marked deterioration in the patient's clinical condition, testosterone therapy was discontinued and a course of radiation therapy to both lung fields was instituted. Portals measuring 9 by 20 cm. were directed anteriorly and posteriorly over both lung fields. A tissue dose of 2,100 r was delivered to the midplane of the lung fields bilaterally in three weeks. The physical factors used were half value layer 1.7 mm. of copper, target skin distance 70 cm., total air dosage 1,800 r in air per portal, treating two of four portals per day. Treatment was completed on March 15, 1952. Approximately two-thirds of the way through the x-ray therapy, 20 mg. of nitrogen mustard was given intravenously. This dose was slightly under 0.5 mg. per kilogram. (The patient's weight at that time was 43 kilograms.) A transitory leukopenia appeared on the ninth day after the nitrogen mustard, and the low point of 2,500 leukocytes was reached at two weeks. The blood count was normal at five weeks. Six weeks after completing the x-ray therapy, the patient was gaining weight rapidly, felt well, and appeared to be in excellent health.

Comparison roentgenograms of the chest made on April 7, 1952 (Fig. 4), demonstrated regression of all the metastases. Films made on May 28, 1952 (Fig. 5), showed disappearance of most of the nodules in both lung fields. By June 17, 1952, the chest roentgenograms appeared entirely normal, and have remained so to date (Fig. 6). All A-Z tests have remained negative, the last two and one-fourth years postoperatively.

One and a half years after operation this patient apparently had a true convulsion. Complete studies were negative, and we are still at a loss to explain what happened. As far as we are able to determine, this patient is well and healthy, with no residual disease.

CASE 2.—Mrs. Q. M., T.U.H. Tumor Clinic No. 53-2801, Chorionepithelioma Registry No. 328, age 38 years, Negro, was delivered of a normal, full-term infant at Temple University Hospital on July 18, 1953. The placenta was described as normal and complete. There was a mild postpartum endometritis, but the patient left the hospital on the fifth day following delivery. She experienced daily bleeding, requiring one to two pads, until almost six weeks post partum. At that time the discharge was dark and she was examined in the Follow-up Obstetric Clinic. A diagnosis was made of a subinvoluted uterus. About one month later (10 weeks post partum) the patient thought she had a normal period. The dark bloody discharge continued, however.

On Nov. 5, 1953 (16 weeks post partum), the patient came to our Accident Dispensary, complaining of "coughing blood and a tumor in the vagina." The hemoptysis had been present for two days.

Physical examination revealed an acutely ill, emaciated Negro woman, who was constantly coughing blood. The temperature was normal and the respiratory rate 28. Râles were present throughout both lung fields. At the vulvovaginal junction, just under the urethra, was found a raised, deep red to purple, granular, and necrotic area about 1½ cm. in diameter. Otherwise the pelvic examination was not remarkable. The uterus was at the upper limits of normal size and seemed soft. A biopsy of the vaginal lesion was taken.

X-ray of the chest revealed well-circumscribed, multiple nodular densities throughout both lung fields, typical of widespread pulmonary metastases (Fig. 7).

The results of laboratory tests showed hematocrit 33 per cent, hemoglobin 10.1 Gm., white blood cells 8,300. Urinalysis and serologic tests were negative. Uric acid was 3.6 mg. per cent, total serum protein 6.1 Gm. per cent, globulin 1.5 Gm. per cent, and albumin 3.6 Gm. per cent.

Studies of pulmonary function showed the following:

Minute volume, 17 L.	Normal	6- 12
Breathing rate, 48	Normal	15- 20
Total volume, 350 c.c.	Normal	500-1,000
Maximum breathing capacity, 24 L.	Normal	80- 130
Reserve, 29 per cent	Normal	90
Vital capacity, 700 c.c.	Normal	2,500-4,000
Blood oxygen saturation, 88 per cent		

It was obvious that the patient's respiratory function was severely impaired from all points of view. The admission diagnosis of choriocarcinoma with pulmonary and vaginal metastases was verified on review of the vaginal biopsy.

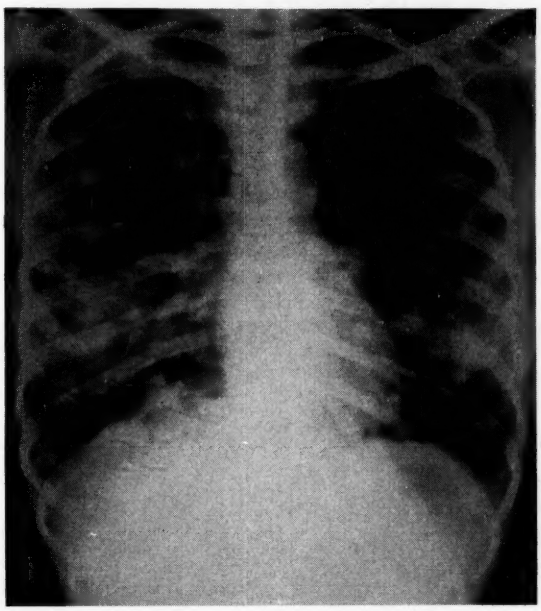

Fig. 7.—Chest film taken Nov. 5, 1953, showing the density of the metastases.

Tissue Report.—Tissue fragments were covered on one surface by an intact and orderly squamous epithelium, beneath which there were collections of tumor cells embedded in and surrounded by fibrin and red blood cells. The neoplastic cells formed irregular strips or villus-like structures; their cytoplasm tended to be clear or brightly eosinophilic, and their nuclei were vesicular for the most part and possessed prominent single red-staining nucleoli. In some cells the nuclear chromatin was dispersed as relatively coarse granules against the nuclear membranes. Pleomorphism of nuclei was prominent. The cells imitated syncytial and Langhans elements of the chorionic villus (Fig. 8).

Bronchoscopic secretions showed no evidence of tumor cells and needle biopsy of the lungs revealed only lung tissue.

Endocrine Studies.—These investigations were performed in the laboratory of Endocrinology of Temple University Hospital under the direction of Bernhard Zondek, using his methods as described.[14, 15, 16]

1. Urine in dilution of 1:2,000 gave a positive pregnancy reaction. That means that 1 L. of this urine contained 200,000 Rb. U. of chorionic gonadotrophin (C.G.). Since one Rb. U. is equal to 5 M.U., this urine contained 1,000,000 M.U. C.G. per liter.

2. Spinal fluid: Intravenous injection of 2.5 c.c. of undiluted spinal fluid into mature rabbits gave a positive reaction. This meant 400 Rb. U. equaled 2,000 M.U. per liter. A positive reaction in an infantile mouse with 0.5 c.c. of spinal fluid is indicative of mole or choriocarcinoma.

3. Bronchial secretion: The A-Z test was positive with 0.6 c.c.

Operation.—On Nov. 12, 1953, under epidural anesthesia, a complete hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus was essentially as described and the ovaries were cystic. The vaginal metastatic lesion was excised.

Special Endocrine Studies Done by Dr. Bernhard Zondek Using the Operative Material.—One gram of endometrium was available, and the chorionic gonadotrophin was extracted. This extract was injected in increasing amounts into 15 infantile mice. It was found that the extract of 2 mg. (fresh endometrial tissue) contained 1 M.U. of follicle-stimulating hormone (FSH), whereas 8 mg. contains 1 M.U. of luteinizing hormone (LH), which means that the pregnancy reaction can be achieved with 8 mg. of endometrium. Zondek previously reported[15] the following values in a case of proved choriocarcinoma:

1 M.U. of FSH in 1 mg. of endometrium and
1 M.U. of LH in 1.25 mg. of endometrium.

Normally Zondek found that these values hold for normal chorionic tissue:

7 weeks' pregnancy shows 7 mg. of endometrium containing 1 M.U. of LH
11 weeks' pregnancy shows 30 mg. of endometrium containing 1 M.U. of LH
Term pregnancy shows 100 mg. of endometrium containing 1 M.U. of LH.

Thus the finding of 1 M.U. of LH in 8 mg. of endometrium proves active chorionic tissue.

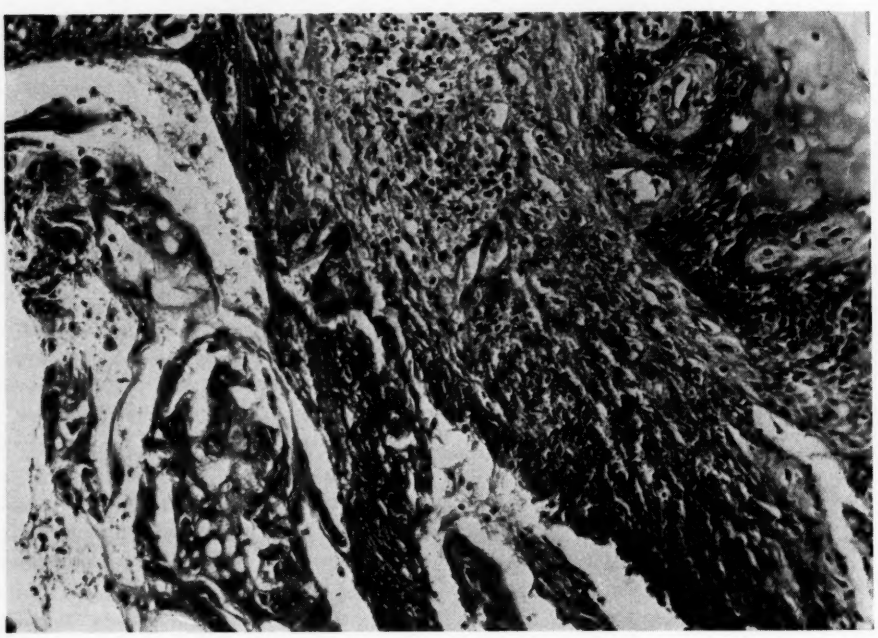

Fig. 8.—Biopsy of vaginal growth.

Using small pieces of tissue from the vaginal metastatic lesion, Zondek implanted these in increasing amounts into the thigh muscles of infantile mice. A 100 mg. piece of tissue gave a definite positive A-Z reaction. Zondek felt that this was proof that the tissue was metastatic from choriocarcinoma.

Zondek further aspirated the follicle fluid from the many small cysts in the removed ovaries. With 1.2 c.c. of the fluid injected into infantile mice a definite reaction was

achieved: the uteri enlarged, and the ovaries contained blood points and many corpora lutea. Follicle fluid never contains chorionic gonadotrophin, it is found only in lutein cysts of moles or choriocarcinoma.[14]

Pathological Report.—The vaginal metastatic lesion presented the identical tumor pattern previously seen on biopsy. No tumor could be found in the uterus. (Serial sections were made and every thirtieth cut was stained and examined.) The endometrium in most areas was replaced by sheets of decidual cells. The ovaries contained multiple small follicular cysts and showed nodular areas of lutein-cell proliferation.

Postoperatively the patient was quite dyspneic and her pulse rate was 116-120. She required continuous oxygen, besides the usual supportive postoperative medications. On the fourth postoperative day there was no change in her vital capacity, and her condition was precarious. At this time, Nov. 16, 1953, radiation therapy was initiated to the metastatic disease in the lungs. Anterior and posterior portals, each 13 by 28 cm., were directed over each lung field, with a midline separation of 3 cm. Conventional 250 kv. therapy of half value layer 1.7 mm. of copper was used at a focal distance of 70 cm. A tissue dose of 2,500 r was delivered to the middle of the thorax over four weeks, in 150 r daily increments.

Nitrogen Mustard.—Two weeks following operation, while the patient was receiving external irradiation to the lungs, she was given 17 mg. of nitrogen mustard intravenously. Following this she improved markedly. Her appetite had returned to normal and her strength allowed walking about the ward. Three weeks following operation, the vital capacity had returned to normal, although x-ray studies of the lungs indicated no change in the metastatic elements. About five weeks postoperatively we noted a small mass about 2 cm. in diameter located in the hypogastric fossa. This felt like a lymph node and it increased to 5 cm. in size in a six-day interval. So, on Dec. 21, 1953, external irradiation to the pelvis

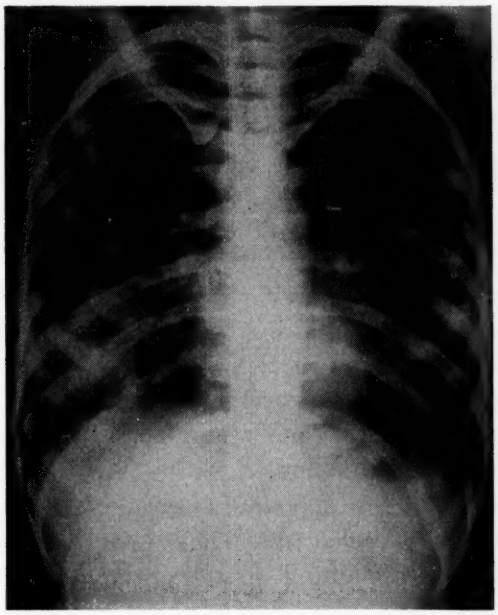

Fig. 9.—Chest film taken on Feb. 5, 1954, one week before death.

was started. Rotation therapy was used of the same quality described above, at a focal distance of 85 cm. A tissue dose of 144 r was administered daily and treatment was given every day except Sunday. The size of the portal was 10 by 16 cm. with the longer dimension paralleling the axis of the body. A tissue dose of 3,600 r was administered throughout the pelvis and treatment was completed on Jan. 18, 1954.

The patient was discharged from the hospital seven weeks after admission while still receiving x-ray therapy. The A-Z test was negative for the first and only time.

She was followed in the Gynecologic Tumor Clinic at weekly intervals. Her titer never changed from a positive of 1:100. She gradually grew weaker (Fig. 9), was readmitted to the hospital, and died on Feb. 14, 1954, three months following operation.

Autopsy (A7758).—An autopsy was done on Feb. 14, 1954, and the relevant gross and microscopic findings were related to the lungs, breasts, thyroid and pelvic tissue.

The left lung weighed 700 Gm. The tracheobronchial tree contained frothy fluid and both lungs showed considerable edema. Studding the outer and cut surfaces of both lungs there were multiple nodules or plaques averaging about 1 cm. in diameter, but varying from 9 mm. up to 2 cm. in size. Some of these areas were purple red in color and hemorrhagic, while others were yellow and soft. The pulmonary tissue was generally firmer than normal and its sectioned surfaces had a yellowish-white appearance, suggestive of diffuse fibrosis. Multiple sections of the lungs on microscopic study presented a variable picture. There were areas of necrosis and of fibrous scarring intermingled with areas of chronic interstitial pneumonitis and interstitial fibrosis. Areas of recent and old hemorrhage, some of which assumed the pattern of recent and old infarctions, were prominent. The intact alveoli contained lipid-laden macrophages or edema fluid, and in some a hyaline membrane, reminiscent of the so-called "asphyxial" membrane, was identified. Metastatic tumor tissue, similar to that described in the vaginal material, was also present. The tumor collections in some areas were accompanied by hemorrhagic necrosis, and in other places they were embedded in fibrous tissue. This diffuse, although variable, pulmonary pathology was considered responsible for respiratory failure and death. The identifiable tumor cells were viable. Factors leading to these pulmonary changes could be multiple; among them there might be considered irradiation effects, infection, hemorrhage into and around the tumor, or breakdown and necrosis of tumor tissue with subsequent irritative effect on the surrounding pulmonary parenchyma. Perhaps the cause of death could be related to failure of general body defenses or whatever factor it is that is responsible for death in generalized carcinomatosis. Fibrosing changes were present in the breasts and thyroid.

Deep in the true pelvis adjacent to the inner aspect of the ilium on the right side there was a 1.5 cm. hemorrhagic area, which on morbid microscopy consisted of widely dilated vessels, some of which exhibited recent thrombosis. A small focus of tumor was identified in this tissue, but it was not possible to determine whether it was between vessels or intraluminal.

Comment

These two cases are of considerable interest from the clinical, pathological, and therapeutic standpoints. Following the spontaneous evacuation of a benign hydatidiform mole in January, 1951, two subsequent curettages within five months revealed proliferative, nonsecretory endometrium. The subsequent development of a choriocarcinoma (one year after evacuation of the mole) presumably followed a second pregnancy.

The difficulties in making a diagnosis from curetted material are well illustrated here; the first case revealed tumor only in the myometrium, and the second failed to show any remaining primary tumor. The hormonal studies rounded out the usual clinical picture of choriocarcinoma.

While we have no histologic proof (in the first case) of pulmonary metastases, the roentgen interpretation, the clinical course, and the biological tests support their presence. There were identical findings in the lung fields of the second case, where we did have histologic proof of their existence. Both women were dying of pulmonary metastases, and our observations would not support any suggestion of spontaneous regression.

Whether radiotherapy was of any value in treating choriocarcinoma of the lung was not apparent in the literature. Much of the information on the subject of radiosensitivity and curability of choriocarcinoma was scarcely more than hearsay. Accordingly, after examination of documented concepts, it was thought best to depart from tradition.

There is a virtually untouched and yet promising field of potentiation of radiation effect on tumors by the administration of some substance capable of influencing tumor biology. Experimental work along this line has been done by Kaplan.[5] It is our belief that nitrogen mustard had such potentiation in tumor biology. It has been so used in a variety of cases by the Department of Radiotherapy over the past three years. The combination of nitrogen mustard and x-ray therapy was followed by the disappearance of the pulmonary metastases in the first case and the survival of this patient, now over two and one-half years.

The second patient demonstrated remarkable improvement for a short time and her A-Z test became negative. The difference in response to treatment in these two cases might be an illustration of that intangible something called "host resistance."

We are indebted to Dr. Joseph C. Stasney for the history and tissue of the mole in Case 1.

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Discussion

DR. ALLAN C. BARNES, Cleveland, Ohio.—Early in World War II the Chemical Warfare Service brought the nitrogenous analogues of mustard under official scrutiny, and contracted for their investigation. In the course of such investigations, the therapeutic potentials of these materials, as well as their possible war uses, became apparent. The blanket of secrecy, however, had descended on the medical as well as the military applications. Thus it came about that, while the first patient was treated in 1942, this method of therapy was not mentioned in the medical literature until 1946. In April of that year Gilman and Phillips, acting officially for the Section on Pharmacology of the Chemical Warfare Service, published in *Science* a summary of the work of many investigators over the previous four years relating to the fundamental medical properties of the nitrogen mustards. Two months later the Chairman of the Committee on Growth of the National Research Council published in the *Journal of the American Medical Association* a summary of the previously "classified" reports

from many clinics on the therapeutic uses of these materials. The marked nucleotoxic effect of the mustards was early noted, and both of these summaries alluded to the similarity between x-ray and intravenous nitrogen mustard in their effect on tissues.

Intravenous mustard quickly found its place as a palliative weapon and was used chiefly against lymphomas. Its use for inoperable pulmonary lesions has been reported since 1949. In 1950, however, C. T. Klopp made one of the most important of all contributions to the chemotherapy of cancer, when he and his co-workers reported on the intra-arterial administration of this material. Klopp started with the stated premise, "The synergistic action of HN_2 and roentgen rays has been demonstrated," and he referred to the fractional intra-arterial administration of mustard as "chemical radiation."

The point of distinction is, of course, that nitrogen mustard attacks the first epithelial surface it passes. Administered intravenously it is total body therapy, although chiefly filtered out in the pulmonary system. Administered intra-arterially it will attack those lesions which are supplied by the arterial system selected, and has little effect on the venous side of the capillary bed. Larger total doses per kilogram of body weight are therefore possible without the same depressive effect on the hemopoietic system.

Many people in this room have undoubtedly used mustard, either intravenously or intra-arterially, as a form of palliation. Our own particular interest has been with its intra-arterial administration—since the pelvis lends itself well to localized arterial attack—and in our selected group of 20 patients, as well as in the animal studies being carried out under the direction of Dr. Richard Boiman, we have been concerned with dosages and the sequence of therapies combining irradiation and nitrogen mustard.

This experience during the past two years would probably have led us to employ the arterial route in these two women, since the pulmonary artery is so casually approached in this day and age. We would re-treat our patients sequentially with fractional doses, so that the total amount administered would be larger. Our animal studies are prompting us to precede the x-ray with the nitrogen mustard, rather than vice versa, and—had the patient's initial response given us faith in this agent for this particular diagnosis—we would have treated the site of the primary lesion also. One might question these aspects of the treatment of these women.

Drs. Beecham, Peale, and Robbins are not presenting a study in therapy, however, but two case reports which are provocative and interesting; and the authors' fundamental attitude deserves nothing but applause. The 2,500 r delivered to these pulmonary lesions represents a good average for intrathoracic x-ray. It is also, by the way, approximately the dosage that can be delivered to the mid-abdominal plane in a patient with metastatic carcinoma of the ovaries. Yet such therapy is far less than a cancerocidal dose, and the authors have made the commendable effort to supplement this inadequate dose with mustard. Differences in individual modalities or techniques are less important than the basic recognition that, in the face of our inadequate radiation, some supplementation is necessary.

DR. W. NORMAN THORNTON, JR., Charlottesville, Va.—The authors are to be congratulated on the completeness with which they have studied and reported upon their 2 patients with choriocarcinoma. They have pointed out some of the pitfalls in diagnosis, and some of the unusual pathologic and biologic features of this highly malignant tumor.

Our experience with choriocarcinoma, as reported by Williams before this Association in 1942 (AM. J. OBST. & GYNEC. 45: 432, 1943), has been very discouraging. All 4 of our patients died with widespread metastases. There seemed to be some temporary regression of the pulmonary metastases in one patient treated with x-ray, although she died of brain metastases within a few weeks.

Our therapeutic roentgenologist, Dr. George Cooper, agrees with the clinical impression that nitrogen mustard may enhance the effectiveness of radiotherapy in the treatment of some tumors. The combination of nitrogen mustard and radiotherapy has been used in the treatment of primary and metastatic pulmonary tumors during the past four years. Palliation has been accomplished in a number of patients, but in no instance have we noted the disappearance of the pulmonary lesion.

The response of the authors' first patient to this combined method of therapy is provocative of considerable speculation. We would like to consider that this patient had metastatic choriocarcinoma which was highly sensitive to x-ray therapy, or that the radiosensitivity of the tumor was enhanced by nitrogen mustard. One must not forget, however, that occasionally a particular tumor will respond in an unusual manner.

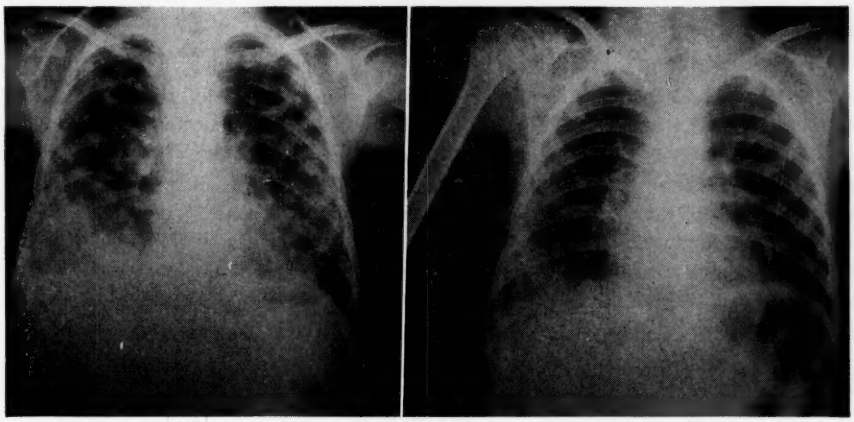

Fig. 1.—Contrast in chest x-rays taken before roentgen therapy and three months afterward in a case of Ewing's tumor at the age of 7 years.

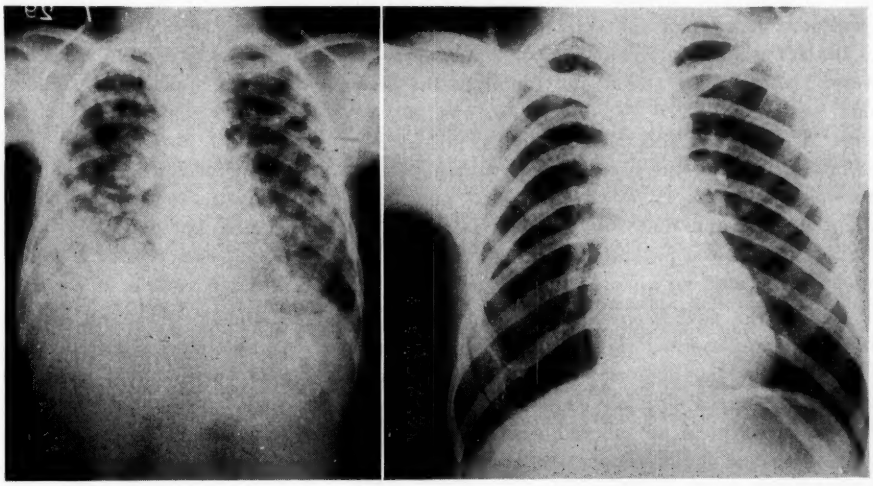

Fig. 2.—Contrast in chest x-rays taken before therapy and eighteen years later.

This unusual response is illustrated by the case of a 7-year-old girl, x-ray No. 45,977, with Ewing's tumor of the right seventh rib with widespread pulmonary metastases. She was cyanotic and considered to be in the terminal stage of her illness when x-ray therapy was given in July, 1932. She received only 800 r in air through each anterior and posterior portal measuring 15 by 20 cm. Films of the chest made prior to treatment and three months later (Fig. 1) show regression of the tumor. The initial film of the chest and one taken 18 years later, showing no evidence of tumor and regeneration of the seventh rib, appear in Fig. 2.

The authors' paper is significant in pointing out the importance of making available to the patient any form of therapy which may be helpful, no matter how hopeless the outlook would seem to be.

DR. J. MASON HUNDLEY, JR., Baltimore, Md.—This paper on metastatic chorionepithelioma stimulated me to review the incidence of chorionepithelioma and hydatiform moles on the obstetrical and gynecological services at the Hospital of the University of Maryland. Through the kindness of Dr. Louis Douglass and Dr. Frank Kaltreider, a review of approximately 56,000 obstetrical patients was carried out. Twenty hydatiform moles and 1 chorionepithelioma were found. In reviewing approximately 35,000 cases on the gynecological service, 3 supposed chorionepitheliomas were found. I would like to analyze the essential data in these reports and show you the errors in diagnosis.

The first patient was admitted to the hospital in marked shock, with evidence of intra-abdominal hemorrhage. A laparotomy revealed a ruptured right tubal pregnancy. The microscopic examination showed a most unusual trophoblastic reaction, so marked that the inexperienced pathologist made a diagnosis of chorionepithelioma. Of course a chorionepithelioma may arise wherever trophoblastic tissue may occur—for example, in a teratoma of the testicle, occasionally in the ovary, and more frequently in the tube when ectopic pregnancy exists. On further histological examination the excessive trophoblastic reaction was thought to be in the realm of normalcy. The patient's subsequent progress showed the correctness of the latter diagnosis.

The second patient was a Negro woman, very obese, who came to the hospital on account of vaginal bleeding. Her history revealed that she was 51 years of age and had menstruated regularly, with the exception of having missed the period just prior to her admission. Her youngest child was 14 years of age. Pelvic examination showed the uterus slightly enlarged, and on curettage considerable material was obtained which proved to be old decidual tissue. A diagnosis of miscarriage was then made. Following discharge from the hospital bleeding continued for several weeks. On readmission another curettage revealed numerous small fibroid tumors, several of the submucosal type. It was felt that the continued bleeding was due to the submucosal fibromas, and a panhysterectomy was performed. On examination of the uterus trophoblastic tissue was found in the myometrium, and a diagnosis of chorionepithelioma was made. The Friedman test was positive for a short period, but later became negative. I feel that this patient had a miscarriage, submucosal fibromas, and metastatic trophoblastic tissue in the myometrium with a positive pregnancy test. I do not believe the process was malignant since we know that metastatic trophoblastic tissue may be found in normal pregnancy and that this in itself is not sufficient evidence for a diagnosis of malignancy. At present the patient has had no more vaginal bleeding, and repeated pelvic examinations have revealed no abnormality. The pregnancy tests became normal in a short period.

I believe the next 2 cases are undoubtedly chorionepithelioma. The first patient, aged 30 years, had been treated in the tuberculosis division of the Baltimore City Health Department for presumable pulmonary tuberculosis, although tubercle bacilli could never be found in the sputum. Repeated x-ray examinations of the lungs revealed increasing areas of density which were not typical of tuberculosis. Her general condition rapidly grew worse, she lost weight, and had a cough productive of copious blood-tinged sputum. She was admitted to the medical service of the University Hospital, and in spite of all supportive measures died four days later. During the period of hospitalization pregnancy tests were done and found strongly positive. Examinations of the lung showed increasing pathologic signs—râles, evidence of consolidation, and so forth. A partial autopsy was performed which, unfortunately, permitted only examination of the chest contents. Here was found what was considered metastatic chorionepithelioma. There were no symptoms suggesting pathology in the generative tract, and no irregularity of menstrual bleeding. In spite of the lack of pelvic symptoms, I would be inclined to believe that the primary focus was trophoblastic tissue in the uterus existing from her last pregnancy, which had terminated in the birth of a normal child seven and a half months previously. Unfortunately a curettage was not performed at autopsy.

In this case the diagnosis of chorionepithelioma is unequivocal, although the primary focus is not definitely known.

The last case to be discussed is that of a woman approximately 42 years of age. Her first admission was to the surgical division for a tumor of the left breast. A diagnosis of malignancy was made and a radical mastectomy, with axillary dissection, was performed. The tumor proved to be a scirrhous carcinoma. About four weeks following the mastectomy she was readmitted to the hospital, complaining of profuse vaginal bleeding. Her history showed nothing suggestive of pregnancy, and her youngest child was 9 years of age. On pelvic examination the cervix was found to be patulous; the uterus was about twice its normal size, soft and symmetrical; the vagina revealed no pathology. A provisional diagnosis of miscarriage was made. On curettage a considerable quantity of decidua-like tissue was removed, which on microscopic survey was typical of chorionepithelioma. X-ray examination of the chest showed areas suggestive of metastasis. Because of this, it was thought that radical removal of the pelvic organs was contraindicated and that intracavitary radiation would be the procedure of choice. Accordingly, the patient received 6,500 mg. hr. of radium, from multiple sources. This therapy proved futile, for the uterine enlargement and bleeding continued, and the metastatic lesions in the lungs advanced with great rapidity. The patient showed progressive signs of inanition and collapse, the outstanding symptom being cough, with copious blood-tinged sputum, in which cellular elements were demonstrated. She died three and a half months following her first admission for the breast tumor. A complete autopsy revealed the lungs to be solid with metastatic chorionepithelioma. The pituitary gland was twice its normal size; this finding was considered to be the result of gonadotrophic stimulation. This patient showed two types of malignant lesions—scirrhous carcinoma of the breast and a chorionepithelioma of the uterus. Her last known pregnancy had been approximately nine years before admission. A radical panhysterectomy should have been performed, but the outcome would probably have been the same. The late Dr. James Ewing said that he had been unable to find any record of a patient with chorionepithelioma who was cured by operation. According to others, a small percentage of cures have been obtained by radical operation, and certainly this procedure is the treatment of choice. One of the most interesting observations in this case is the apparent longevity of the trophoblastic tissue from which the growth developed. Here we have a chorionepithelioma developing nine years after the last known pregnancy, although it is possible that an unrecognized miscarriage could be the focus for the development of the chorionepithelioma. From numerous observations it appears that the trophoblastic tissue is capable of great longevity. Reis (quoting from Williams' *Obstetrics*) reported a patient in whom epithelioma developed 17 years after her last pregnancy.

We have presented 4 cases in which a diagnosis of chorionepithelioma was made. In 2 of these the evidence was not sufficient to support the diagnosis, but the remaining 2 are definitely chorionepitheliomas.

It is generally felt that mistaken diagnoses of chorionepithelioma are fairly common. Apparently many pathologists do not realize that metastatic trophoblastic tissue may be found with normal pregnancy.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Beecham quoted Dr. Ewing's statement that he had never seen a patient with genuine choriocarcinoma get well. I am convinced that that is an incorrect generalization. We recorded in our paper in May a good many recoveries which occurred in cases which our Committee had decided were genuine choriocarcinomas. We went back to those 13 patients who got well (out of 74 verified cases of choriocarcinoma) and tried to convince ourselves that they were not genuine choriocarcinomas, but we could not do it. I am sure that they were.

Dr. Beecham's paper deals only with the therapy, and more particularly with the possible value of nitrogen mustard. In treating this highly malignant disease, which generally kills the patient within six months of its detection, it certainly is perfectly justfiable to use any form of therapy that is at all rational. I do not know whether Dr. Beecham has collected all the cases in which the use of nitrogen mustard has been reported. I have encountered a few reports of that sort, just as I have encountered reports of the treatment of this disease

by large doses of testosterone or large doses of estrogen and, of course, by x-ray therapy for the pulmonary metastases. From the standpoint of drawing conclusions it is unfortunate that the clinician often fires off all possible therapeutic guns. He is likely to use large doses of testosterone or estrogen simultaneously with radiation and, in a few cases, with nitrogen mustard as well.

For instance, I have just received some slides from a case of choriocarcinoma in which the patient is apparently still well after a great many months, although she had pulmonary metastases. This patient received nitrogen mustard, but also had a full course of radiation.

This whole question of metastases is a very mystifying one. We get "metastases" of normal trophoblastic tissue in normal pregnancy, and benign hydatidiform mole can in rare cases be transported to the lungs and sometimes through the general circulation. Dr. Eastman will remember a case we had in Baltimore of a benign hydatidiform mole, in which histologically proved benign hydatidiform molar tissue was transported to the lungs and to the spinal cord, with no histologic evidence of malignancy at all.

In a paper published in the AMERICAN JOURNAL last May we discussed a group of metastatic lesions which disappeared—some spontaneously and some after x-ray therapy—even in cases of genuine choriocarcinoma. This aspect of our paper was very ably discussed by Dr. Arneson. To show the difficulties of this problem I have just received slides from a case which I think is a perfectly benign hydatidiform mole, in which metastasis was suspected in the lungs. The appearance of the pulmonary lesion was accompanied by a high spiking temperature. The patient received radiation and she is well. I do not believe this patient had a choriocarcinoma, and I suspect that she had an inflammatory lesion in the lung. Yet cases of that kind get into the literature as cases of cured carcinoma. Dr. Beecham, I think, is wise in merely presenting this case, and in not drawing any immediate conclusions as to the value of this form of therapy.

DR. BEECHAM (Closing).—Dr. Novak has stated that some cases in the Registry have been treated with nitrogen mustard. Since these cases reported today are in the Registry, I am wondering if they are not the same ones.

Dr. Barnes has contributed to our knowledge of the experimental use of nitrogen mustard. It appears possible, by employing the technique outlined, to raise the dosage of nitrogen mustard to a specific organ. It is hoped that these additional features as outlined by Dr. Barnes may be employed further in the treatment of pulmonary metastases from choriocarcinoma.

PRIMARY CARCINOMA OF THE VAGINA*

FRANK R. SMITH, M.D., NEW YORK, N. Y.

(From the Departments of Gynecology at Roosevelt Hospital, Gynecology and Obstetrics at New York Lying-In Hospital, and Gynecology at Memorial Center for Cancer and Allied Diseases)

THE paucity of occurrence in any one clinic of primary cancer of the vagina probably best explains the differences in the published statistics on the subject. In addition, differences in data available, methods of therapy used, years selected for study, the personal equation of interpretation, and differences in criteria used set a questionable value on these so-called comparable statistics.

This presentation is not intended to offer salvage statistics for comparison with those of other clinics, but is rather to analyze our own available material, especially for factors influencing prognosis, flaws in therapy, and for theorizing on possible improvement in management.

Although secondary and metastatic tumors of the vagina are more frequently encountered than primary vaginal lesions, and may present some of the same problems of therapy, this discussion is concerned only with primary malignant tumors of the vagina. Primary vaginal cancer is here considered as arising anywhere in the vaginal wall from the apex of the vagina to the hymen, with the cervix free from disease (usually proved by biopsy) unless the patient has been previously seen with localized vaginal cancer that has later extended to the portio vaginalis of the cervix. Cancers of the urethra are excluded, as are other lesions of the vulvovaginal mucocutaneous junction external to the hymen site.

Incidence

The incidence of this relatively rare condition is low, and has been quoted by two well-known statisticians as 2 per cent[1] and 4 per cent[2] of all cancers of the female genital tract. Kottmeier[12] places the incidence at 1 to 2 per cent of malignant tumors of the female genital tract. Because of the rarity of the lesions, many textbooks and authors mention it briefly, or merely include it with secondary lesions.[3-10]

Table I shows the incidence of primary cancer of the vagina in relation to all cancers of the female genital tract during twenty-year periods in each of the three hospitals where the author attends.

Table II shows the ratios of cancer of the corpus to cancer of the cervix, and the ratios of cancer of the vagina to corpus and cervix cancer in each of these three hospitals.

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

TABLE I. RATIO OF PRIMARY CANCER OF VAGINA TO TOTAL CANCERS OF FEMALE GENITAL TRACT (TWENTY-YEAR PERIODS) IN THREE NEW YORK HOSPITALS

HOSPITAL	TOTAL CARCINOMA OF GENITALS	PRIMARY CARCINOMA OF VAGINA		RATIO OF VAGINA TO TOTALS
		NO.	PER CENT	
Roosevelt 1932-1952	682	7	1.0	1: 98
New York Lying-In 1932-1952	1,467	5	0.34	1:295
Memorial 1927-1946	6,050	109	1.7	1: 55

TABLE II. RATIO OF CANCER OF CORPUS TO CANCER OF CERVIX AND RATIO OF PRIMARY CANCER OF VAGINA TO CANCER OF CERVIX AND TO CANCER OF CORPUS (TWENTY-YEAR PERIODS) IN THREE NEW YORK HOSPITALS

HOSPITAL	TOTAL CORPUS	TOTAL CERVIX	RATIO CORPUS TO CERVIX	RATIO VAGINA TO CORPUS	RATIO VAGINA TO CERVIX
Roosevelt 1932-1952	210	318	1:1.5	1:30	1: 45
New York Lying-In 1932-1952	467	649	1:1.4	1:93	1:129
Memorial 1927-1946	970	3,671	1:3.7	1:9	1: 34

Because of rather marked differences in incidence and ratio, numbers of patients available, the twenty-year period selected, and methods of management, it seemed advisable to limit the statistical analysis to the 109 patients treated under the same conditions and all at Memorial Center. The twenty-year period of 1927 to 1946, inclusive, was selected because in 1947 a radical change in therapy was instituted. The patients treated from 1947 on will be discussed later.

Factors in Prognosis

In a previous publication based on 57 patients studied, certain prognostic factors in primary cancer of the vagina were noted by the author.[11] These were: (1) age of the patient, (2) location of the lesion in the vagina, (3) parity, (4) pathologic type, (5) rapidity of growth, and (6) stage of the disease when first treated.

On the basis of the study of this larger series of 109 patients with proved primary cancer of the vagina treated at Memorial Hospital (1927 to 1946), these possible factors were reinterpreted. This group of 109 patients compares favorably with the number of patients studied in recent publications by several authors, as shown in Table III.

TABLE III. PREVIOUS REPORTS ON PRIMARY CANCER OF THE VAGINA

AUTHOR	YEAR PUBLISHED	YEARS STUDIED	PATIENTS
Messelt[13]	1952	1932-1945	78
Kaiser[14]	1952	1927-1950	55
Bivens[15]	1953	1931-1951	46
Singh[16]	1951	1925-1949	21
Huber[17]	1950	1922-1949	152
Way[10]	1948	1930-1946	44
Douglas[18]	1954	1944-1952	8
Palmer and Biback[19]	1954	1919-1952	75
Memorial Hospital	1954	1927-1946	109

The average age of these 109 patients was 54.2 years. The majority of patients who developed primary cancer of the vagina (71.5 per cent) were between 40 and 70 years of age. In this series their prognosis was actually not as good as that of the patients under 40 and over 70 years of age based on a five-year survival rate. Nearly two-thirds in the series were over 50 and their prognosis was as good as that of the patients under 50. In Table IV it should be noted that 34 patients, or 31.1 per cent lived more than 5 years. Ten of the 34 patients, however, are now dead and only 24, or 22 per cent, are alive at the present time. This survival rate will be used from here on.

TABLE IV. AGE DISTRIBUTION AND ITS EFFECT ON LENGTH OF LIFE FROM DATE OF FIRST TREATMENT AT MEMORIAL HOSPITAL

AGE IN YEARS	INCIDENCE		LIVED MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Under 30	5	4.5	1	20.0
30-40	12	11.0	6	50.0
40-50	24	22.0	5	20.4
50-60	21	19.2	8	38.5
60-70	33	30.3	8	24.2
70 Plus	14	12.8	6	42.8
Total	109	100.0	*34	31.1
40-70	78	71.5	21	26.6
20-40	17	15.5	7	41.1
60-80	47	43.1	14	29.7
Under 50	41	37.6	12	29.3
Over 50	68	62.3	22	32.3

*Ten patients now dead.

Most statistical reports designate the location of the lesion as anterior or posterior wall, upper, lower, or middle third, and attach importance to the fact that the lymphatic drainage from the outer third tends to be to the inguinal and femoral nodes; the upper third follows the drainage from the cervix to hypogastric, iliac, and obturator nodes; the middle third may drain either way, usually tending to drain to the deep pelvic nodes. The decision on location of the primary site is quite dependent on the personal interpretation of the individual doing the evaluation. It may well be that prognosis is less affected by the location than by whether the lesion is papillary and growing into the lumen of the vagina, or is infiltrating the submucosa, or encircling the vagina eventually. The recent studies of Douglas[18] seem to add new evidence to what many have felt (or there would have been fewer local excisions), namely, that the disease is often limited to the vagina and adjacent tissues even though it seems more extensive.

Table V shows that in this series lesions in the upper third have a somewhat better prognosis than lesions in the other locations. Unfortunately, the patients with these more favorable lesions make up only one-fourth of the total patients.

TABLE V. EFFECT OF LOCATION OF PRIMARY VAGINAL LESION ON LENGTH OF LIFE FROM FIRST THERAPY

LOCATION	INCIDENCE		ALIVE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Outer third	29	26.5	2	6.8
Middle third	48	44.0	12	25.0
Upper third	27	24.7	10	37.0
Entire vagina	5	4.5	0	0.0
Total	109	100.0	24	22.0

Table VI indicates that while more than two-thirds of these women had had pregnancies, there was little or no difference in the proportion alive five years or more.

TABLE VI. EFFECT OF PARITY ON LENGTH OF LIFE FROM DATE OF FIRST THERAPY AT MEMORIAL HOSPITAL

PARITY	INCIDENCE		ALIVE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Nulliparous	32	30.4	7	21.8
Parous	73	69.5	17	23.2
Total	109*	100.0	24	22.0

*Pregnancies not known in four patients.

Table VII does not confirm the former contention that the anaplastic type was more favorable than the Grade I and Grade II types. Adenocarcinoma continues in this series to be the most favorable group.

TABLE VII. PATHOLOGY OF PRIMARY CANCER OF THE VAGINA—DISTRIBUTION OF PATHOLOGICAL TYPES AND THEIR SIGNIFICANCE AS TO LENGTH OF LIFE FROM FIRST THERAPY WITH ALL TYPES OF THERAPY USED

PATHOLOGIC TYPE	INCIDENCE		ALIVE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Epidermoid, Grade I	5	4.5	1	20.0
Epidermoid, Grade II	71	65.1	19	26.7
Epidermoid, Grade III	18	16.1	1	5.5
Adenocarcinoma	9	6.4	3	33.3
Sarcoma	6	5.5	0	0.0
Total	109	100.0	24	22.0

Table VIII (using the empirical six months) shows that patients with a longer interval between the first symptom and first treatment fared better than those with less than six months' interval. This suggests rapidity of growth as a factor in prognosis. One may not conclude that delay in treatment after the first symptom is advocated by the author.

TABLE VIII. EFFECT OF RAPIDITY OF GROWTH ON LENGTH OF LIFE AS SHOWN BY THE INTERVAL BETWEEN THE TIME OF FIRST SYMPTOMS AND THE TIME OF FIRST THERAPY

INTERVAL	INCIDENCE		ALIVE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Less than six months	58	53.2	10	17.2
More than six months	51	46.7	14	27.4
Total	109	100.0	24	22.0

Management and methods of treatment should influence prognosis.

TABLE IX. METHOD OF THERAPY AND LENGTH OF LIFE FROM DATE OF FIRST TREATMENT IN PATIENTS WITH POSITIVE NODES WHEN FIRST SEEN

METHOD	INCIDENCE		LIVED MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Irradiation only	20	55.5	1	5.0
Surgery (inadequate) only	3	8.3	0	0.0
Irradiation and then surgery	12	33.3	2	16.0
No therapy	1	2.7	0	0.0
Total	36	100.0*	3	8.3

*None alive today.

36 of 109 in series, or 33.3 per cent } had palpable nodes at time of first treatment.
36 of 85 dead, or 42.3 per cent }

Of 36 patients with the disease sufficiently advanced to have palpable nodes when first seen at Memorial Hospital, only 3, or 8.3 per cent, lived five years (Table IX). None are alive today. Thus, 33.0 per cent of the entire series and 42.3 per cent of the patients now dead had palpable nodes when first seen. Irradiation and surgery (inadequate in this group) gave the best prognosis.

As with cancers everywhere, the stage of the disease when first treated is perhaps the most important factor in prognosis.

More than one-third of the patients in this series had advanced lesions when they were first seen (Table X). Salvage statistics will be definitely influenced by the proportion of advanced lesions in any series selected.

TABLE X. INFLUENCE OF STAGE OF DISEASE ON LENGTH OF LIFE FROM TIME OF FIRST THERAPY AT MEMORIAL HOSPITAL

STAGE WHEN FIRST SEEN	TOTAL		ALIVE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Localized	66	60.5	24	36.3
Advanced	43	39.4	0	0.0
Total	109	100.0	24	22.0

Methods of Therapy

No attempt has been made to analyze the doses of irradiation used. Kottmeier[12] has stated that the mucosa of the vagina will tolerate 25,000 to 30,000 gamma r. Certainly we have used no such dosage in this series for cancer of the vagina. Probably our doses were inadequate, yet 11 of 109 patients, or 10.0 per cent, developed fistulas. The author[20, 21] was able to show that of patients with cancer of the cervix, the untreated patients had about twice the incidence of fistulas of irradiated patients, and felt that the fistulas were due to the advanced stage of the disease rather than to the irradiation therapy. The surgery employed in this series was in no instance radical in the present-day evaluation. The term "more extensive" refers to patients who had more than local excision.

Table XI shows the comparison of types of treatment in all patients in the series. Measured by the proportion of five-year survivals, more extensive surgery alone or in combination with irradiation gave, in general, the best results.

TABLE XI. TYPE OF THERAPY COMPARED AS TO LENGTH OF LIFE FROM TIME OF FIRST THERAPY AT MEMORIAL HOSPITAL

TYPE OF TREATMENT	INCIDENCE		SURVIVED MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Irradiation only	73	66.4	20	27.3
Irradiation plus inadequate surgery	23	21.1	5	21.7
Irradiation plus more extensive surgery*	3	2.7	2	66.6
More extensive surgery* only	7	6.4	7	100.0
No therapy	3	2.7	0	0.0
Total patients	109	100.0	34	31.0

*More than local excision; still not radical.

Table XII is concerned with 85 pateints who are all dead. Only 10, or 11.7 per cent survived five years and these were in the groups treated by irradiation only, or in combination with local excision or other inadequate surgery.

TABLE XII. TYPE OF THERAPY COMPARED AS TO LENGTH OF LIFE FROM TIME OF FIRST TREATMENT AT MEMORIAL HOSPITAL
Patients All Dead

TYPE OF TREATMENT	INCIDENCE		LIVED MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Irradiation only	61	71.7	8	13.1
Irradiation plus inadequate surgery	20	23.5	2	10.0
Irradiation plus more extensive surgery	1	1.1	0	0.0
More extensive surgery only	0	0.0	0	0.0
No treatment	3	3.5	0	0.0
Total	85	100.0	10	11.7

Table XIII deals with 24 patients now alive more than five years. Ten patients, however, are alive with disease. Only 14 patients are alive without evidence of disease today. In this small living and favorable group, irradiation alone gave the best results.

TABLE XIII. TYPE OF THERAPY COMPARED AS TO LENGTH OF LIFE FROM TIME OF FIRST TREATMENT AT MEMORIAL HOSPITAL AND NUMBER OF PATIENTS FREE FROM DISEASE OF THOSE
Alive Five Years

TYPE OF TREATMENT	INCIDENCE		NO EVIDENCE OF DISEASE MORE THAN FIVE YEARS	
	NO.	PER CENT	NO.	PER CENT
Irradiation only	12	50.0	10	83.3
Irradiation plus inadequate surgery	3	12.5	2	66.6
Irradiation plus more extensive surgery*	2	8.3	1	50.0
Extensive surgery* only	7	29.0	1	14.2
No therapy	0	0 0	0	0.0
Total	24	100.0	14	58.3

*More than local excision; still inadequate. Only 14 patients of 109, or 12.8 per cent, alive with no evidence of disease five years from treatment.

Table XIV emphasizes our inability to combat primary cancer of the vagina by the methods used in this series of 109 patients. Certainly one must conclude that if 85, or 77.9 per cent, have already died, and 10, or 9.1 per cent, with disease will die, some better plan of management for this 87.1 per cent must be devised.

TABLE XIV. CLASSIFICATION OF STATUS OF 109 PATIENTS BASED ON FIVE-YEAR INTERVAL FROM DATE OF FIRST TREATMENT

CLASSIFICATION	NUMBER OF PATIENTS	PER CENT
X. Dead with disease	85	77.9
Dead in less than five years	75	68.8
A. Dead but lived five years	10	9.1
B. Alive with disease	10	9.1
A and B	20	18.3
Dead or will die, X and B	95	87.1
Five-year survival	34	31.1
Alive five years	24	22.0
Alive with no evidence of disease five years	14	12.8 absolute rate

TABLE XV. PATIENTS TREATED BY RADICAL SURGERY, DEAD, 1947-1954

PATIENT	AGE	OPERATIONS	IRRAD.	COMPLICATIONS	LOCATION	STAGE	DEATH—POSTOPERATIVE TIME
1. St.B., L.	59	Posterior exenteration	None	Perforated stomach	Posterior wall	Advanced	Perforated stomach, 2 weeks
2. E., G.	51	Total exenteration	Radium, 3 years	Rectal slough post irradiation	Upper third, rectovaginal	Advanced	With cancer 3 years post operation, 6 years post irradiation
3. V., N.*	3	Posterior exenteration Local excision 2 years before	Radium, 2 years	None	Total	Advanced	With sarcoma, 18 months
4. H., A.	52	Anterior exenteration, vulvectomy	None	Old coronary	Outer third	Advanced	Cardiac death, 2 weeks post-operatively
5. E., H.	49	Exploratory	None	None	Middle third and vulva	Advanced	With cancer, 6 months post-operatively
6. T., L.	35	Hysterectomy, removal of nodes and vagina; ligation of right iliac and hypogastric veins	None	Swelling, right leg	Middle and upper thirds	Advanced	With cancer, 2 months post-operatively
7. H., W.	50	Hysterectomy, removal of nodes, partial colectomy	Radium, 1 year	Rectovaginal fistula, repair 4 months postoperatively	Entire	Advanced	With cancer, 6 months post operation, 18 months post irradiation
8. A., M.	50	Total exenteration, vulvectomy, partial colectomy	None	Demerol addict, large fibroid	Outer third	Advanced	With cancer, 3 years post-operatively, and coma

*Sarcoma botryoides, all others epidermoid. Previous radium in 3 patients, 2 of 3 had fistulas, no postoperative irradiation.

TABLE XVI. PATIENTS TREATED BY RADICAL SURGERY, ALIVE, JUNE, 1954

PATIENT	AGE	TYPE SURGERY	IRRADIATION	COMPLICATIONS	LOCATION	STAGE	INTERVAL POST OPERATION
9. H., M.	53	Hysterectomy, nodes, vagina	None	Swelling in legs, slight	Upper third	Localized Negative nodes	No evidence of disease 17 months postoperatively Slight swelling legs
10. K., F.	61	Hysterectomy, nodes, vagina	None	None	Upper third	Negative nodes	No evidence of disease 1 year, 8 months post-operatively
11. T., O.	50	Hysterectomy, nodes, vagina	None	Uterovaginal fistula repaired 2 months postoperatively Nephrectomy 3 months postopera-tively	Middle third	Negative nodes	No evidence of disease 4 years, 2 months post-operatively
12. B., B.*	44	Total exenteration	6 x-ray treatments before Memorial Hospital	Bilateral hydro-nephrosis	Upper third, bladder, rectum	Moderately advanced	No evidence of disease 3 years, 5 months post-operatively
13. C., C.†	66	Radical cervicectomy, vagina and nodes	None	Ileus postoperatively	Upper third	Negative nodes	No evidence of disease 2 years, 10 months post-operatively
14. P., A.	51	Posterior exenteration	None	None	Posterior wall, upper third	Negative nodes	No evidence of disease 1 year, 8 months post-operatively
15. G., R.	63	Posterior exenteration	None	Tracheostomy	Lower third, rectal wall	Negative nodes	No evidence of disease 4 years, 4 months post-operatively
16. R., M.‡	73	Radical vaginectomy and nodes	X-ray	None	Upper third	Negative nodes	No evidence of disease 4 years, 1 month post-operatively
17. H., M.	51	Radical vaginectomy, hysterectomy and nodes	None	None	Upper posterior third	Negative nodes	No evidence of disease 6 years postoperatively

*Spindle-cell sarcoma, all others epidermoid carcinoma.
†Supracervical hysterectomy for fibroids 7 years before Memorial Hospital.
‡Total hysterectomy for fibroids 25 years before Memorial Hospital.

In an attempt to improve the existing poor results and with a better knowledge of electrolyte balance and of supportive measures of modern surgery, all patients coming to Memorial Hospital with primary cancer of the vagina since 1947 have been treated with more radical surgery as the initial therapy. Of 17 patients so treated, 8 are dead and 9 are alive with no evidence of residual or recurrent disease as of June, 1954. This is not intended to give survival rates for comparison because a five-year period has not elapsed for most of these patients.

Table XV lists the eight dead patients.

Table XVI lists the nine living patients.

Comment

Certain features of this brief study are of interest:

1. The 8 dead patients were all in advanced stages when first operated on, whereas the 9 living patients had more localized lesions.

2. None of the survivors had positive nodes, but neither did any of the patients now dead, at the time of operation. This supports somewhat the suggestion of Douglas[18] that the disease tends to remain limited to adjacent structures for longer periods than had formerly been supposed.

3. Complications were frequent and are listed in the tables. Only 6 of 17 patients (35 per cent) escaped complications and one of these had simply an exploratory operation.

4. Three patients now dead had radium therapy before coming to Memorial Hospital, and 2 of the 3 had fistulas. There was one fistula in a nonirradiated patient. Two of the living patients had x-ray before coming to Memorial Hospital. No patient had postoperative irradiation.

5. The disease was epidermoid carcinoma in 15 patients. Patient No. 3 was a 3-year-old child with sarcoma botryoides, with previous radium and local excision. Patient No. 12 had spindle-cell sarcoma.

6. In 8 of 9 patients now living the lesion was above the outer third of the vagina. In the patients now dead the disease was too advanced when first seen to permit accurate localization of origin.

Summary and Conclusions

1. The incidence of the disease has been discussed.

2. The criteria for accepting each case as a primary cancer of the vagina have been stated.

3. An analysis of 109 consecutive patients with proved cancer of the vagina has been presented.

4. The stage of the disease when first treated is the most important prognostic factor.

5. Location of the lesion above the outer third of the vagina gave a less unfavorable prognosis than location in the outer third.

6. Parity plays no part in prognosis.

7. Pathologic grades vary in prognosis in different series. They are of less prognostic value than gross growth-pattern tendency of the lesion.

8. Rapidity of growth influences prognosis.

9. Too conservative and inadequate initial therapy, whether irradiation, surgery, or a combination of both, has been the stigma of the past.

10. The nature and location of the disease suggest that, in spite of possible complications, more radical surgery should be utilized earlier in an attempt to solve this hitherto unsolved problem.

11. Certainly no one type of therapy is applicable for all types and stages of this disease, and the selection of patients is in order for optimum treatment.

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55 East 73rd Street
New York, N. Y.

Discussion

DR. FRANKLIN L. PAYNE, Philadelphia, Pa.—My intense interest in primary carcinoma of the vagina is due largely to therapeutic frustration in the past. During the preceding ten years we have seen 8 instances of primary invasive vaginal carcinoma. Five were treated by radiation, 1 by radiation and surgery, and 2 by radical surgery. The only survivor received interstitial and external radiation six years ago and now presents no evidence of disease. The microscopic picture in this case was interesting in that it showed a glandlike arrangement of mucus-secreting cells.

In a review of this material, 2 instances of primary intraepithelial vaginal carcinoma were encountered. Both patients complained of minimal abnormal staining, and examination of each revealed a small granular area on the upper posterior vaginal wall which oozed on trauma. In both cases the biopsies showed changes identical with those of intraepithelial cervical carcinoma. One was treated by partial vaginectomy four years ago, with no recurrence, and the other received a surface radiation dose of 4,000 r by means of a vaginal bomb, with no recurrence. General acceptance of the thesis that intraepithelial carcinoma of the cervix should be treated actively indicates like management for similar lesions of the vagina, when good fortune permits their discovery.

Dr. Smith's series of 109 patients with primary vaginal carcinoma is, with one exception (Huber's), the largest to be reported recently. Particularly impressive is the 100 per cent follow-up observation extending from 1927 to the present time.

The first group discussed consists of 109 patients and the second of 17 patients. The first group is then divided into two subgroups: (1) those with palpable nodes (36 in number), of whom only 3 (8.3 per cent) survived five years; and (2) those without palpable nodes (73 in number), of whom 31 (42.5 per cent) survived five years or more. For the entire group the therapeutic measures with their results are listed in four categories: (1) surgery (7 cases, 7 survivors); (2) radiation plus extensive surgery (3 cases, 2 survivors); (3) radiation plus inadequate surgery (23 cases, 5 survivors); and (4) radiation alone (73 cases, 20 survivors). Either surgery alone or radiation plus extensive surgery, which the essayist described as "inadequate" in the light of modern knowledge, gave the best results.

The over-all five-year survival rate was 31 per cent but this was later reduced to 22 per cent by the death of ten of these patients. Of the 24 patients now alive five or more years following treatment, 10 still have cancer and presumably will die of the disease. This reduces the ultimate achievement rate from 22 per cent to 12.8 per cent—a depressing state of affairs.

The second group of 17 patients has been treated by modern radical surgery, and 9 of the 17 (53 per cent) have remained alive and free from any evidence of disease for intervals varying from one to six years following this new plan of management. At the moment this is indeed a rosy picture—one that will stir the imagination of all and stimulate resolute activity on the part of many who are called upon to deal with this problem. It can only be hoped that the picture will remain as promising as the years go by. We should recall, however, that 7 out of 7 patients in Dr. Smith's first group survived for five years following extensive but "inadequate" surgery—but that 6 of these subsequently died of cancer. It should also be remembered that adequate surgery for primary vaginal malignancy is radical surgery in every sense of the word. It should be undertaken only by specialists highly trained in this particular field and under environmental circumstances that are ideal as they pertain to the care of the patient before, during, and after operation.

DR. R. A. KIMBROUGH, Philadelphia, Pa.—In support of Dr. Smith's statement concerning the relative infrequency of primary carcinoma of the vagina, I have had but 2 personal cases in an experience of 30 years. Peculiarly, both of these were apparently adenocarcinomas presumably arising from remnants of Gartner's duct or from aberrant cervical glands in the vagina.

The first patient, Mrs. G. G., a nullipara, aged 25 years, was referred by Dr. E. R. Brubaker of Reading, Pennsylvania, in June, 1951. In November of 1950 he had excised an elevated granular lesion about 0.5 cm. in diameter from the upper right wall of the vagina. The local pathologist made a diagnosis of a relatively differentiated squamous carcinoma. Dr. Emil Novak interpreted the lesion as carcinoma of Wolffian-duct origin and expressed the opinion that the wide local excision offered a reasonable chance of cure. Six months later, however, a similar lesion appeared high on the left wall of the vagina. Microscopic study of this lesion revealed an undifferentiated carcinoma.

Because of this recurrence, I performed a radical removal of the adnexa, uterus, and upper two thirds of the vagina, along with a complete pelvic node dissection. No residual tumor was found in the vagina or other of the removed structures. The patient was last seen in June of this year; she is well and presents no suspicion of recurrence.

The second patient was referred by Dr. Fred B. Nugent of Reading, Pennsylvania. Mrs. H. B., a 41-year-old para i, was admitted to the Pennsylvania Hospital in April, 1952. She had been treated for an intense vaginitis since 1947. A biopsy was taken of an elevated granular lesion of the right vaginal fornix in 1947, and again in 1949. Nothing more than inflammatory tissue was found. A third biopsy in August of 1951 revealed

an adenocarcinoma which Dr. Novak believed to be of Wolffian origin. Intensive x-ray therapy produced an excellent immediate response. Within six months, however, the opposite vaginal fornix and the rectovaginal septum became involved.

Total pelvic exenteration was performed on April 18, 1952. The lesion had extended to the cervix and to the rectovaginal septum, but metastasis to regional lymph nodes could not be demonstrated. Her early convalescence was uneventful, but unfortunately she succumbed on the twenty-seventh postoperative day to a massive hemorrhage into a retroperitoneal urinary abscess.

These 2 cases suggest that this particular type of lesion tends to remain localized for long periods and that less radical removal might have been elected.

Our own experience with radiation therapy has been almost routinely disappointing, and we agree with Dr. Smith that the surgical approach constitutes the treatment of choice in all operable lesions.

DR. EMIL NOVAK, Baltimore, Md.—Dr. Kimbrough has included in his discussion of vaginal cancer a rather peculiar and rare variety of primary carcinoma of the vagina in which we have been very much interested—the kind which arises from remnants of the mesonephric duct, or the Wolffian duct, and which occurs in the upper part of the vagina and also in the cervix. This group of lesions was discussed in a paper presented, in collaboration with J. Donald Woodruff and E. R. Novak, before the American Gynecological Society in May. Among the cases which we included were the 2 cases that Dr. Kimbrough has mentioned today.

It is worth remembering that if one sees a granular lesion in the vaginal fornix which is suggestive of cancer, it may be of mesonephric origin, and either benign or malignant. One finds in the base of some of the ulcerative lesions seen in this area ducts representing the vestiges of the mesonephric structures. I think we should remember also that there is a group of cases, very rare—even more rare than sarcoma botryoides—which clinically resemble the latter perfectly. They appear as grapelike lesions of the cervix or uppermost portion of the vagina and occur not infrequently in infants or children, but histologically they have not the slightest resemblance to sarcoma botryoides. They present the structure of mesonephric tubules. In this same region we sometimes see tumors which resemble the so-called mesonephroma of Schiller as it occurs in the ovary. In our paper we showed that some of the mesonephric lesions in the ovary, cervix, or vagina may contain an admixture of the so-called clear-cell carcinomas of the ovary, and we interpreted this as indicating that these two tumor types are histogenetically closely allied.

I want to mention one more point that has nothing to do with this particular group of tumors, but does have something to do with the therapy of carcinoma of the vagina. I have seen only one case of carcinoma of the vagina that I thought was cured by irradiation, and this case emphasizes a possible hazard of the management of cancer in general. The patient had had irradiation therapy in Detroit thirteen years previously for carcinoma of the vagina, and was apparently well. When I saw her, she had a large cystocele but no sign of vaginal carcinoma. I got the original sections from Detroit, and there was no question about the lesion as having been a genuine epidermoid carcinoma. The cystocele was covered by a very avascular, unhealthy-looking mucosa, so that I was afraid to try to repair it at that time. A couple of years later the cystocele had become very large, and since the condition of the mucosa had improved a cystocele repair was done. Within two months after the operation this patient developed a huge lymphedema of both lower extremities, and died shortly afterward. This case illustrates one of my firm beliefs—that many patients who are clinically cured of cancer by irradiation still harbor live carcinoma cells which are trapped by the irradiation fibrosis, but which may be set free later by biopsy or any other surgical procedure.

DR. SMITH (Closing).—I was interested in Dr. Novak's report of the case in which massive lymphedema of both legs was followed by death from a late recurrence of

vaginal carcinoma. It has always been our opinion that when patients who have been treated for pelvic cancer get swelling of the legs, there is active disease in the pelvis. We used to talk about radiation fibrosis being the cause, but it subsequently was proved in practically every instance that active disease was present.

There were two slides left over, which I had intended to use as an example of swelling of the leg which is due to causes other than carcinoma. The patient had a radical vaginectomy, a hysterectomy, and dissection of the pelvic lymph nodes, and in the course of the operation the internal hypogastric and femoral veins in the same leg were ligated. Films made after injection of the ankle vein with radiopaque iodopyracet showed an anastomosis across the abdominal wall from the vein in the leg. The patient seemed fine except for swelling of the leg, but she lived only three months. At autopsy she was found to have extensive disease with lymphatic blockage, and it was not entirely apparent that the ligation of the vessels caused the swelling.

CARCINOMA OF THE OVARY FOLLOWING HYSTERECTOMY*

VIRGIL S. COUNSELLER, M.D., WILLIAM HUNT, M.D., AND
FRANK H. HAIGLER, JR., M.D., ROCHESTER, MINN.

(From the Sections of Surgery, and of Gynecology and Obstetrics, Mayo Clinic and Mayo Foundation†)

FOR many years it has been the practice of one of us (Counseller) to preserve the ovaries when hysterectomy is performed for a benign condition, provided one or both ovaries appear normal. As far as can be determined from the literature and from discussions with others interested in the subject, there seem to be few established data to justify such a practice except the personal opinion of the surgeon.

The question has been asked many times, "Why should the ovaries be saved if the hysterectomy is performed for a benign condition?" The simplest answer has seemed to be that the patient is a more nearly normal person when they are left than when they are removed, except in extensive endometriosis with very little involvement of the ovaries. Another reason is that frequently the patient requests that the ovaries be left undisturbed if they are normal and there is no cancer. This happens more often in younger patients than in menopausal patients, but even some menopausal patients feel the same way and it is difficult to change their minds. When the patient is unwilling to be castrated, that fact should be recorded in the clinical history and in the surgeon's consultation notes. Similar records should be made also when the surgeon encounters sufficient disease of the ovaries to justify their removal at the time of hysterectomy. The surgeon is not likely to experience legal difficulties if he performs castration when it seems indicated, but some patients are unhappy and mentally disturbed by the procedure.

The question to be answered, therefore, is whether the patient who is undergoing either abdominal or vaginal hysterectomy for a benign condition should be subjected also to castration to prevent subsequent development of carcinoma of the ovary. Since the incidence of the development of carcinoma of the ovary subsequent to hysterectomy had never been determined in our institution, we decided to ascertain this incidence and see whether it would provide an answer to the question.

Observations in 67 Cases

From a series of more than 1,500 cases of proved carcinoma of the ovary during the twenty-three-year period, 1930 through 1952, 67 patients (4.5 per cent) were found who had undergone hysterectomy for a benign condition. To evaluate these cases, three factors seemed to be of importance, namely, the

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

†The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

age of the patient at the time of hysterectomy, the age of the patient at the time carcinoma of the ovary was found, and the interval of time between the hysterectomy and the occurrence of carcinoma of the ovary.

The physiologic activity of the ovary should have considerable influence in determining whether castration should be done in such patients before the climacteric period. This period is certainly a variable one, so that it is not correct to say that it begins at the age of 40 or 44 years or at any other specific age. From Table I it is apparent that only 2 patients in our series of 67 were less than 30 years of age and 20 were in the age group from 30 to 39 years at the time of hysterectomy, while 45 patients were 40 years old or older. The number of patients 60 years old or older was about the same as the number less than 30 years of age.

TABLE I. AGE AT THE TIME OF HYSTERECTOMY

AGE (YEARS)	NO. OF PATIENTS	PER CENT
<30	2	3.0
30-39	20	29.9
40-49	29	43.2
50-59	13	19.4
60+	3	4.5
Total	67	100.0
Mean 44.4 years		
Youngest 28 years		
Oldest 74 years		

As is shown in Table II, only 3 patients (4.5 per cent) were less than 40 years of age at the time carcinoma of the ovary was found, while about 70 per cent were in the age period from 40 to 59 years. Thus, the cases tended to be rather closely related to the period of the menopause and involution of the ovary.

TABLE II. AGE AT TIME CARCINOMA OF THE OVARY WAS FOUND

AGE (YEARS)	NO. OF PATIENTS	PER CENT
<40	3	4.5
40-49	19	28.4
50-59	28	41.7
60-69	13	19.4
70+	4	6.0
Total	67	100.0
Mean 54.6 years		
Youngest 37 years		
Oldest 78 years		

As is seen in Table III, in about 80 per cent of the patients the interval of time between the hysterectomy and the subsequent discovery of carcinoma of the ovary was 5 years or more. A breakdown of the 14 patients in the group with an interval of 0 to 4 years showed that in only 2 patients was the interval less than 1 year, and in 3 patients it was more than 1 but less than 2 years.

TABLE III. INTERVAL BETWEEN HYSTERECTOMY AND FINDING OF CARCINOMA OF THE OVARY

INTERVAL (YEARS)	NO. OF PATIENTS	PER CENT
0-4	14	20.9
5-9	21	31.4
10-14	12	17.9
15-19	13	19.4
20+	7	10.4
Total	67	100.0
Mean 10.2 years		

It is conceded that 67 patients in a series of 1,500 with carcinoma of the ovary over a twenty-three-year period is nothing to be greatly disturbed about; yet if we knew how many women in every 10,000 would have carcinoma of the ovary during their lifetime and especially if we knew at what decade it would be most likely to occur, we could decide more readily whether or not to castrate the patient at the time of hysterectomy for a benign condition than we can decide now on the basis of physiologic function and appearance of the ovaries. Randall and Gerhardt[1] have given us some sound and astonishing data on the probabilities of the occurrence of the more common types of gynecologic malignancy. From their article we quote the following: "We believe, however, the data here presented will provide those interested in the relative frequencies of the different types of gynecologic malignancy with more reliable information than has been available in the past. Since our recommendations usually depend upon our opinion of the possibilities our patients face, agreement regarding the probabilities of malignancy appears desirable." They state, furthermore, "Perhaps the incidence of malignant disease in an organ does justify its removal as a cancer-preventing measure, but we believe we should be fully aware of the actual occurrence rates and the calculated probabilities that malignancy might develop in the tissues or organs under consideration."

In our series of patients, only 4.5 per cent were less than 40 years of age, while 95.5 per cent were 40 years old or older at the time carcinoma of the ovary was found. This approximates rather closely the age distribution given by Randall and Gerhardt. Although only 4.5 per cent of our patients were less than 40 years of age when their ovarian carcinoma was found, approximately 33 per cent were in this age group when they underwent hysterectomy. It appears, therefore, that the age of the patient at the time of hysterectomy should be a factor in determining whether or not castration should be done. Other factors also must be considered. If a young person has a history of malignancy in her family, especially of the pelvic organs, castration should be seriously considered. It should be considered also if the patient has uncontrollable menstrual irregularities. Allan and Hertig[2] obtained a history of malignancy in the families of 12.5 per cent of their patients, and we obtained such a history in 19 per cent of our patients.

We were unable to determine the indications for the original hysterectomy except in 16 of the patients who underwent hysterectomy at our institution. The indications in these cases were prolapse, multiple fibroids, menometrorrhagia, and dysmenorrhea. There were 9 vaginal and 7 abdominal hysterectomies. Only 1 of the 16 patients was less than 40 years of age, and she underwent a vaginal hysterectomy at the age of 33 for uncontrollable menorrhagia and dysmenorrhea. Seven years later, at the age of 40, she was found to have bilateral grade 4 adenocarcinoma of the ovaries. She was living and well 4½ years later. Eleven of the 16 patients died of recurring carcinoma 1 to 2 years after hysterectomy. Fifteen were more than 50 years of age when the ovarian carcinoma was discovered.

The number of benign ovarian tumors which have occurred subsequent to hysterectomy is considerable, but that point is not pertinent to our discussion except from the standpoint of provoking the observation that, if it were the practice to perform bilateral castration when any type of hysterectomy is performed for benign conditions in women past 40 or 45 years of age, there would be fewer subsequent operations for ovarian disease. Thorp[3] found that, of 276 ovarian tumors removed in the period 1945 to 1949 from women who previously had undergone hysterectomy, 10 were malignant, 5 of the 10 representing patients who died of their carcinoma. The time interval between the hysterec-

tomy and the occurrence of the ovarian malignancy varied from 2 to 25 years; this is essentially the same as in our group of 67 cases, in which the interval ranged from 4 to 20 years or more.

Of the 67 patients in our series, 18 were operated on after 1948 and hence were ineligible for a five-year follow-up. Among the remaining 49 patients, 5 were untraced. Of the 44 traced patients, 16 lived 5 or more years after operation for carcinoma of the ovary, giving a five-year survival rate of 36.4 per cent. This corresponds to a rate of 35 per cent observed by Allan and Hertig[2] in 60 patients who had undergone gynecologic operations.

Comment

From this material and the reports of Randall and Gerhardt,[1] Allan and Hertig,[2] Thorp,[3] Crossen,[4] and Greenhill,[5] it appears that if one wishes to prevent ovarian carcinoma subsequent to any type of hysterectomy for benign conditions, then castration of premenopausal and menopausal patients is justifiable. This is particularly true if there is a family history of malignancy. Furthermore, the evidence does not seem to indicate that castration should be performed at the time of hysterectomy in all patients less than 40 years of age, who in our series represented only one-third of the cases. However, if there is a family history of malignancy or a history of undetermined menstrual irregularities, bilateral salpingo-oophorectomy is justifiable. In other instances the ovaries should be normal, grossly at least, if they are to remain in situ.

Since the physiologic and mental disturbances attending castration of a woman in her twenties or thirties constitute a serious problem, the operation should not be done indiscriminately but only after presurgical explanation and discussion of the possibilities and consequences. If patients and relatives understand the facts, they almost always agree that the surgeon may use his own judgment.

The fact that patients 40 years old or older in our series represented only 67.1 per cent of the hysterectomies but 95.5 per cent of the ovarian malignancies makes it seem reasonable to advise castration in that age group. Crossen[4] has advised removal of the ovaries whenever the abdomen is opened in women who are 42 years old or older and who are in the climacteric, unless there is some definite contraindication. Greenhill[5] commented editorially that he agrees with others who remove normal ovaries at the time of hysterectomy in women past 44 years of age. He considered it good prophylaxis.

The treatment of the ovarian carcinomas in our series did not give satisfactory results. It consisted of surgical exploration, with complete removal of the ovaries and excision of peritoneal and omental implants. In some cases segments of small bowel and the sigmoid were excised also. In addition, all patients were given a complete course of x-ray therapy. Some lesions were inoperable. None of the patients were given radioactive gold intraperitoneally. At present some patients who have granular implants throughout the upper part of the abdomen as well as in the pelvis are being given radioactive gold plus a complete course of x-ray therapy extending over a period of approximately 3 weeks; they could not, of course, be included in this study.

Summary and Conclusions

In a series of more than 1,500 cases of proved carcinoma of the ovary during the twenty-three-year period, 1930 to 1952, inclusive, 67 patients (4.5 per cent) were found who had undergone hysterectomy for a benign condition. While approximately 33 per cent of the 67 patients were in the group less than 40 years of age, only 4.5 per cent of the ovarian carcinomas occurred in that age group. The five-year survival rate for 44 traced patients was 36.4 per cent. Except under unusual circumstances it seems doubtful, therefore, whether patients less than 40 years of age who are to undergo hysterectomy for benign conditions should be advised also to have castration to prevent subsequent carcinoma of the ovary. On the other hand, the evidence suggests that one should advise castration for patients who undergo hysterectomy during and after the menopause. This period should be determined on the basis of the clinical evidence presented by the patient.

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Discussion

DR. GEORGE H. GARDNER, Chicago, Ill.—This has been a most interesting and thought-provoking presentation. The question is still unanswered, however, "Shall the ovaries be preserved, when a hysterectomy is performed for a benign condition, if one or both *appear normal, and they are functional?*" Furthermore, this controversy will not be settled readily or soon. Most of us admit to rather strong convictions on this subject, even though they may have been determined by life-long practices and prejudices, rather than by an objective analysis of the available pertinent data, meager as they are.

Dr. Counseller and his co-workers have reported on 67 such patients treated at the Mayo Clinic from 1930 through 1952. It would be interesting to know how many thousands of hysterectomies this group represents, and in precisely what percentage cancer developed. Sixteen of the cases in their series, however, followed hysterectomies at the Clinic, so that we could learn something about the frequency there, if Dr. Counseller would tell us how many hysterectomies they performed in the years 1920 to 1942, inclusive. The number of hysterectomies in those particular years must be compared with their own 16 patients with ovarian cancer *discovered in the period 1930 through 1952*, if one is to determine the true frequency of this complication; may I remind you that there was an average lag of 10.2 years, in the entire series of 67 patients, between the original operation and recognition of the cancer.

It is also interesting that in 9 of these 16 cases the original operation at the Mayo Clinic was a vaginal hysterectomy. One wonders if there was a similar 9 to 7 ratio of vaginal to abdominal approach among all of their hysterectomies performed between 1920 and 1942. A more probable explanation for such a ratio lies in the indications for vaginal hysterectomy. Such an approach is utilized more frequently when ovaries are normal than when adnexa are diseased; consequently one should expect that a larger percentage of ovaries would be preserved during the vaginal operation. Furthermore, it would be interesting to know if those who advocate that ovaries *always* be removed after the age of 42, 44, or any other age, actually always remove them, or always remove them *only*

with abdominal hysterectomies. As a matter of fact, I doubt that many of us remove ovaries, routinely, during a vaginal hysterectomy for procidentia, even in postclimacteric women.

It would also have been interesting to know if these 67 patients had had just one ovary or both ovaries spared at the original operation; and further, whether one or both of the ovaries became cancerous. Some of us are not yet convinced that removal of one ovary reduces by 50 per cent the chance of subsequent ovarian cancer. Another question: Is the likelihood of cancer developing after hysterectomy greater, less, or just the same as in women who have not had such surgery? According to Randall, that probability is never more than 9 per 1,000; at 50 years it is 8 per 1,000, and decreases rapidly thereafter.

Finally, I heartily endorse what I consider to be the essence of Dr. Counseller's conclusions, namely, that in this matter of removing ovaries, *patients must be individualized.* A dictum that they should always be removed after age 44, for example, is fundamentally untenable, because a chief indication for hysterectomy at that age is uterine fibromyomas, and women with such tumors often continue to menstruate much later than the average. Furthermore, the menopause—that is, cessation of menses—is by no means synonymous with complete cessation of ovarian function; in reality such function may continue for months after menstruation stops. Therefore, it is our responsibility to determine for individual patients whether the various discomforts of a prematurely induced climacteric are justified, in view of the real, although very slight, chance that they may subsequently develop cancer of the ovary. Here again Dr. Counseller's experience is comforting to those who do not routinely castrate such women, since his management yielded five-year clinical arrests in 36.4 per cent of those whith posthysterectomy ovarian cancer; indeed that is an enviable record.

DR. J. L. REYCRAFT, Cleveland, Ohio.—It might be of interest to you to know what our experience has been on this subject at the University Hospitals in Cleveland. During a ten-year period from 1944 through 1953, more than 5,000 hysterectomies were performed in our institution. Of these, in 500 cases, or almost 10 per cent, bilateral salpingo-oophorectomy was performed at the time of operation. During that same ten-year period, 9 cases of carcinoma of the ovary were encountered in patients who had had a partial or complete hysterectomy, an incidence of 0.2 per cent.

When the cases of carcinoma of the ovary were analyzed, it was found that only 3 had occurred within ten years after hysterectomy. In 5 the interval was 12 to 19 years, and one occurred 22 years after hysterectomy. Four of the 9 patients were between 45 and 50 years of age, and the remainder were older than 50 at the time of admission.

During the same period of time, 134 other patients with carcinoma of the ovaries were admitted, principally for palliative treatment. In one of these cases carcinoma of the cervix and remaining ovary had occurred 23 years after unilateral oophorectomy and x-ray sterilization; in another, the ovarian cancer followed x-ray treatment of a fibroid 25 years previously.

The salvage rate of 36 per cent in patients with carcinoma of the ovary following hysterectomy for benign conditions, as reported by Dr. Counseller, is remarkable. Our survival rate is 2 out of 9, or approximately 22 per cent.

Dr. Clyde Randall has told us that approximately 70 per cent of all ovarian neoplasms develop before the patient's fiftieth year, and that the chance of development of ovarian cancer after the age of 50 is about nine in a thousand.

Dr. Counseller had only 3 patients (4.5 per cent) who were less than 40 years of age when carcinoma of the ovary was found, while 70 per cent were in the age period between 40 and 59 years. As others have observed, most of the cases occur during the time of the menopause and associated involution of the ovary.

We would be inclined to the opinion that bilateral oophorectomy in a woman who has a hysterectomy between the ages of 40 and 45 should be done only if there is a family history of malignancy; otherwise, we advocate this procedure only after 45 years of age.

Much has been said on the subject of the physical and emotional changes that follow castration, even in the menopause. These symptoms can be controlled in the majority of cases, however, by the judicious use of oral estrogens.

DR. THADDEUS L. MONTGOMERY, Philadelphia, Pa.—What happens to the ovary, or ovaries, when left in situ during the course of an abdominal hysterectomy for benign disease is of considerable interest if one has reliable information on the condition of the ovaries at the time of the original surgery. If one approaches this problem by analyzing a group of lesions which appeared later in life, there is always some question as to the findings at the original hysterectomy.

For this reason, one must agree with Dr. Gardner that this study of Dr. Counseller's would have had greater significance if, from the large volume of hysterectomies performed for benign disease at the Mayo Clinic, there had been a follow-up over a span of five, ten, or more years to determine what had happened to the gonads which were left in place.

It is quite natural, however, that the essayist, on the basis of observations which he has gathered together, should feel disturbed at encountering malignant disease in the ovary which might have been prevented by prophylactic bilateral oophorectomy at the time of previous hysterectomy. If it is the author's thesis that the ovaries must be very carefully inspected, and perhaps occasionally biopsied and bisected before being left in situ at hysterectomy, I heartily agree. If, on the other hand, it is his thesis that the ovaries should be removed prophylactically in *all* hysterectomies for benign disease, I would be inclined to disagree.

There seems to be no logical reason to remove functioning organs because of the possibility that serious disease might occur in them in the future, unless it can be demonstrated that the operation which one is performing is likely to predispose the patient to the occurrence of such disease. In the instance of hysterectomy, one may concede that many operations interfere with the nutrition of the ovary and may lead to more rapid withdrawal of function and an earlier onset of the menopause. I know of no statistics at the moment, however, which suggest that hysterectomy predisposes to neoplastic growth in the ovary. Assuming that the ovaries are normal at the time of operation, it seems unlikely that there is any greater chance of ovarian carcinoma developing in that patient than in the nonsurgical subject at the same age.

For those of us who practice community obstetrics and gynecology, and have the opportunity of following patients who have had a surgical castration before the termination of ovarian function, the significance and value of a maintained ovarian secretion seem very important. The systemic effect and the local tissue regression in the instance of surgical castration is not measurable satisfactorily in terms of hormone assay alone. It may equally well be evaluated by the temperament of these patients and their attitude toward living.

If one subscribes to the thesis of removing at operation those other organs in which cancer is likely to develop in the future, then there are several which are of much greater significance in this category than the ovary. I am thinking particularly of the female breast. After 35 years of age this is the female organ in which cancer is most likely to develop. It has lost its physiologic function after the childbearing period, and is quite amenable to simple mastectomy in a brief time and under the same anesthesia as the hysterectomy is performed.

There seems to be no enthusiasm for the removal of one or both breasts as a prophylactic measure, and I would not want to be misunderstood as recommending this procedure. From the standpoint of mortality figures, however, there would be much more logical support for such an additional operative undertaking than there would be for bilateral oophorectomy. Incidentally, it might be well if the gynecologist would pay more attention to the possibilities of pathologic lesions in the breast at the time of his gynecologic examination and surgical therapy.

In summary, I feel that there is no sensible basis for the policy of removing a normal organ during its period of active function because of the possibility that at some time in the future it might develop disease. The end result of such procedure would be to defeat the very purpose and goal of surgery—that is, eradication of disease and the preservation of function where this is feasible.

DR. CLYDE L. RANDALL, Buffalo, N. Y.—There are some points that need clarification when we start to discuss the prevalence or frequency of cancer, particularly the distinction between incidence and probability that the statistician recognizes.

Data on the relative frequency of a particular type of malignancy as a cause of death do not furnish a good source of information as to the relative frequency of that type of malignancy, because the effectiveness of treatment is going to affect the mortality rate from that particular lesion. It is interesting to note that in New York State the number of deaths from malignancies of the uterus, including cervix and fundus, has decreased rapidly from 31.08 per 100,000 women twenty years ago to 20.58 now. That decline in the mortality rate doesn't represent a decrease in the number of cases; it represents earlier diagnosis and more effective treatment. The number of deaths due to carcinoma of the breast has remained almost exactly the same. Carcinomas of the ovary accounts for a slightly increased number of deaths.

The New York State Health Department has recorded all cases of malignancy reported over a fourteen-year period, among two and a half million women. At no time has the annual incidence of ovarian malignancy risen above 40 per 100,000—approximately one case per 2,500 women per year.

Such figures regarding incidence are entirely different from data regarding "probability." The latter indicate the chance that a particular individual has of developing a particular disease after any particular age. If we knew that at the Mayo Clinic there had been 50,000 hysterectomies and if we knew the ages of groups of women at the time of hysterectomy, by calculating the number of years women would probably live after those ages, we should be able to estimate how many women in such a group of 50,000 might ultimately develop a carcinoma of the ovary. We now know the chance that the average woman has of developing an ovarian malignancy in the remaining years of her life, however. We know, for example, that, above the age of 40, 9 women per 1,000 will develop cancer of the ovary; above 60, it is 6 per 1,000, and at the age of 70 there are still 3 chances in 1,000—0.3 per cent probability—that a woman might still develop a malignancy of a preserved ovary.

Another suggestion I would like to make is that we do not, as yet, have any very definite information as to the advantages of preserving the ovary when hysterectomy is performed at the menopause. Many feel very strongly that routine castration should not be employed, but they find it a little difficult to be very emphatic about the advantages of preserving the ovary, particularly when it is so simple to give replacement therapy. I have no very clear conception as to how many women, after the menopause, really suffer as a result of a lack of estrogens. Their symptomatology is subject to many factors. There are, of course, a few anatomic evidences, particularly the atrophic changes; but I am under the impression that relatively few women develop an appreciable or marked degree of atrophic change referable to a lack of estrogen.

I do not believe anyone has ever demonstrated satisfactorily how long the ovary that we carefully preserve at the time of hysterectomy is going to continue to function. We might well ask whether there are technical points in our management of the ovarian pedicle which affect the length of time that the preserved ovary will function. It is my current thought that, by doing an abdominal hysterectomy, we can possibly avoid some of the situations that are likely to follow a vaginal hysterectomy that would tend to shorten the life of the ovary. It seems important to remember that, if we are going to preserve ovaries, we ought to employ an operative technique calculated to disturb the ovarian blood supply as little as possible.

DR. COUNSELLER (Closing).—Dr. Gardner, Dr. Reycraft, Dr. Montgomery, and Dr. Randall have brought out several points that should be studied and reported. I presume that what actually stimulated me, more than anything else, to undertake this study was the return within the past two years of patients who had recurring carcinoma of the ovary, for whom I could do so little. They could have been well for many years to come if I had taken out the ovaries at the time of hysterectomy, even though they were apparently normal at that time. Also, I have had some letters from former colleagues asking me whether the ovaries should not be removed more often when hysterectomy is performed in later periods of life. Such a question is hard for me to answer. I hope all of you realize that I do not advocate castration of all patients on whom hysterectomy is performed for benign conditions. Each case must be evaluated carefully.

It is true that, if we had analyzed all the cases in which hysterectomy was done and those in which one ovary was removed, and made a comparative study, we would now have more nearly accurate data. The statistical problem in such a procedure, however, would have been overwhelming. The suggestion was advanced that we select for study all patients with carcinoma of the ovary who had previously undergone hysterectomy, either at our clinic or elsewhere. Such a base of selection simplified the problem considerably. Many of these patients, of course, underwent hysterectomy in their home locality.

Finally, I might remark that if I can find some energetic fellow in our section who has the time, I will ask him to study all these cases. It will require a man with plenty of time, because it will keep him intensely busy for a long time. Maybe, after his long toil, he can give us a better answer.

CONSERVATIVE TREATMENT OF CARCINOMA IN SITU OF THE CERVIX*

A Clinical and Cytopathological Study

THOMAS C. PEIGHTAL, M.D., WALTER W. BRANDES, M.D., PH.D.,
DAVID B. CRAWFORD, JR., M.D., AND EVELYN S. DAKIN,
NEW YORK, N. Y.

(From the Gynecological Service and the Department of Pathology, The Roosevelt Hospital)

AN ANALYSIS of the questionnaires sent out in 1952 by both Carter[1] and Davis[2] indicates that carcinoma in situ of the cervix is treated in most clinics by hysterectomy of varying extent, some using a more radical type of extirpation than others. Some preserve the adnexa in the younger age group, while others remove the ovaries in all cases. A few use x-ray and radium therapy.

During the past six years on the Gynecological Service of The Roosevelt Hospital, we have experimented with various types of biopsies in evaluating the pathology found in all cases with positive cytology smears. Gradually these biopsies have become more and more extensive. The multiple punch method was replaced by the ring procedure, with which we endeavored to excise the whole squamocolumnar junction (as described by Ayre[3]). This more recently has been replaced by the cone biopsy, which not only widely excises the squamocolumnar junction, but also removes a cone of tissue including most of the gland-bearing area of the cervical canal approximately to the internal os. This same purpose can be accomplished by amputation of the cervix if this method is preferred (Fig. 1).

The multiple punch biopsy proved to be inadequate for confirmation of positive cytology in the case of preclinical cancer, and in ruling out the possibility of early invasion. Similarly, we now believe the same criticism can be leveled at the shallow ring biopsy. We came to feel that we are much less likely to miss a small area of invasion when we remove adequate tissue, as in the cone biopsy, and when this tissue is carefully studied by multiple section technique.

This procedure, we have found, presents certain advantages. It serves not only to prove the presence of carcinoma in situ, but also shows whether or not, and to what extent, the cervical glands are involved. Any areas of near or frank invasion can be seen as well. In addition, after such a diagnostic study, the plan for treatment would seem more logical and less likely to be erroneous. If the lesion is intraepithelial or with minimal gland involve-

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

ment, a simple hysterectomy will suffice; while if the gland involvement is extensive, or if there is any question of early invasion, a wider hysterectomy (such as Te Linde[4] has described) or even a radical node dissection can be carried out. In the latter instance, if one prefers, the patient can be treated with x-ray and radium. At least one will avoid the embarrassment of doing a simple hysterectomy for carcinoma in situ diagnosed by punch or shallow ring biopsy, and then discovering invasive carcinoma in the cervix of the hysterectomy specimen.

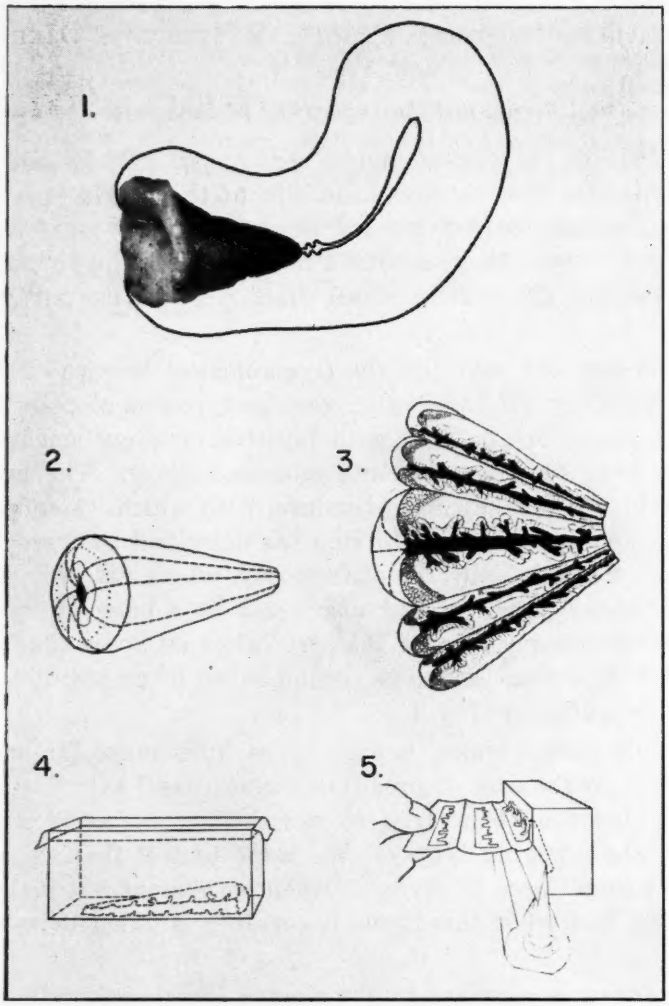

Fig. 1.—*1*, Approximate size and shape of the cone in relation to the uterus. *2* and *3*, Cervical cone specimen is divided longitudinally into multiple cuts (approximately 8 to 10 segments). Following processing and embedding, *4*, each segment is completely serially sectioned (ribboned), as in *5*. Serial strips are mounted from these ribbons. Selections are taken at equal intervals throughout the entire circumference, including the area of the squamocolumnar junction as dotted, *2*. Approximately 30 to 100 mounts are prepared on each case.

The study of these cervical ring and cone specimens, together with multiple section observation of the hysterectomy specimens subsequent to such

biopsies, forms the background of this paper. It supports our observation that certain cases of carcinoma in situ may be treated conservatively, when desired, by doing nothing more than an extensive cone type of excision (similar to that described by Martzloff[5]) or cervical amputation, provided a careful cytological follow-up ensues. Additional evidence for this statement is to be found in our cases so treated and followed.

For the past three years, our Gynecological Service has had the advantage of a well-equipped laboratory of cytopathology under the direction of Dr. Walter W. Brandes, Attending Pathologist, and Miss Evelyn S. Dakin, co-authors of this paper. During this period, 7,805 cytology tests were taken on a group of 5,847 patients which involved the study of 16,965 individual smears. Approximately 70 per cent of these were private patients and the remaining 30 per cent were clinic patients. This series has been classified according to the descriptive classification which has been employed in our laboratory of cytopathology (Table I).

TABLE I. CYTOLOGIC CLASSIFICATION

NORMAL	Absence of abnormal cells		A
	Variable morphology within normal limits		B
INFLAMMATORY	Nuclear change suggesting hyperactivity	Moderate	A
		Marked	B
ANAPLASTIC	Change suggestive of a formative stage of cancer	Moderate	A
		Marked	B
MALIGNANT	Cells exhibiting morphology of *early* malignancy		A
	Cells exhibiting malignant morphology		B
UNCLASSIFIED	Cells of indefinite nature but appear benign		A
	Cells suspicious of malignancy but inconclusive		B

Positive smears (i.e., classified as anaplastic or malignant) were found in 71 patients whose cervices were not clinically suspected of harboring a malignant lesion (1.2 per cent or 1 in 82 cases). For this study, 14 cases have been discarded because of incomplete data and, in 7 additional cases, subsequent biopsy showed degrees of anaplasia short of carcinoma in situ, so that 50 cases of this lesion are available for use in this report (Table II). Of these, 22 showed surface epithelial changes only (called strictly intraepithelial carcinoma by some observers as Javert[6]), 19 had glandular involvement as well (called true carcinoma in situ by Javert[6]), and 9 had lesions which not only involved the glands but also minimally invaded the stroma.

Biopsy studies were done in 10 cases from multiple punch specimens. Ring excision specimens were used in 24 cases. Larger cone specimens were used in 13 cases, and in 3 cases the specimens for study were obtained by partial amputation of the cervix.

Treatment of these 50 cases has varied over the period reported, but in general may be said to have become gradually more conservative as the efforts

TABLE II. CORRELATION OF CYTOLOGY AND PATHOLOGY

PATHOLOGY	CYTOLOGY					TOTAL
	ANAPLASTIC		MALIGNANT		UNCLASSIFIED	
	A	B	A	B	B	
Anaplasia	3	1	2	1	0	7
Intraepithelial carcinoma	1	4	7	8	2	22
Intraepithelial carcinoma with gland involvement	2	4	5	8	0	19
Intraepithelial carcinoma with gland involvement and ? early invasion	0	0	0	8	1	9
Total	6	9	14	25	3	57
	15		39			

to obtain a more adequate biopsy specimen have increased. Postoperative multiple section study of the cervices of those uteri which were removed after an extensive ring, cone, or partial amputation type of biopsy had been done revealed that, in most instances, no residual disease remained (Table III). No residual disease was found in 21 of 25 specimens from hysterectomy done after an extensive biopsy procedure. The remaining 4 patients, subsequently found to have residual disease, showed anaplastic or malignant cells cytologically after the biopsy excision procedures, and prior to the hysterectomies. After investigation of these cases it was noted that the original biopsy specimens were inadequate—that is, were received in pieces and broken—or that the laboratory did not receive the entire specimen and complete serial sectioning was not done. We believe that this may account for the presence of residual disease in the hysterectomy specimens.

TABLE III. NO RESIDUAL DISEASE IN HYSTERECTOMY SPECIMEN

PATHOLOGY	TYPE OF BIOPSY PRIOR TO HYSTERECTOMY		TOTAL
	RING	CONE	
Intraepithelial carcinoma	8	3	11
Intraepithelial carcinoma with gland involvement	3	3	6
Intraepithelial carcinoma with gland involvement and ? early invasion	3	1	4
Total	14	7	21

As would be expected, in all instances where the punch biopsy was employed, the hysterectomy specimen revealed residual disease.

The desirability of conservative measures in handling carcinoma in situ may at times be most pressing, particularly in the young and recently married

TABLE IV. NO OPERATION OTHER THAN BIOPSY
(Cytology Follow-up Negative to Date)

PATHOLOGY	TYPE OF BIOPSY					TOTAL
	RING	CONE	AMPUTATION	PUNCH AND AMPUTATION	RING AND AMPUTATION	
Intraepithelial carcinoma	4	2	2	0	0	8
Intraepithelial carcinoma with gland involvement	3	0	1	2	1	7
Intraepithelial carcinoma with gland involvement and ? early invasion	0	0	0	0	0	0
Total	7	2	3	2	1	15

woman who is anxious to preserve her childbearing function. Since most patients with this lesion are under 40, this problem is encountered not infrequently. The average age incidence in our group was 38 years. There were 8 patients in their twenties and 21 patients under 35 years of age.

Emboldened by our findings of no residual disease after extensive biopsy procedures in both the in situ lesions limited to the epithelium and those where the cervical glands have become involved, we have followed 15 cases which have had no other procedure done but a wide ring, a deep cone, or a partial amputation of the cervix. To date, all have remained cytologically negative, smears having been taken every one to four months. Three of these patients were in their twenties, 9 in their thirties, and 3 in their early forties. Eight have been followed for less than one year, but 4 have been followed between one and two years, and 3 for over two and one-half years (Table IV).

TABLE V. RÉSUMÉ OF TREATMENT

PATHOLOGY	TYPE OF TREATMENT						TOTAL
	BIOPSY EXCISION ONLY	HYSTERECTOMY		HYSTERECTOMY (RADICAL, WITH LYMPHADENECTOMY)		X-RAY AND RADIUM	
		NO RESIDUAL	RESIDUAL	NO RESIDUAL	RESIDUAL		
Intraepithelial carcinoma	R 4 C 2 A 2	R 8 C 3	P 1 R 1 C 1				P 1 R 13 C 6 A 2
Total	8	11	3	0	0	0	22
Intraepithelial carcinoma with gland involvement	R 3 A 1 PA 2 RA 1	R 3 C 3	P 4 R 1	C 1			P 4 R 7 C 4 A 1 PA 2 RA 1
Total	7	6	5	1	0	0	19
Intraepithelial carcinoma with gland involvement and ? early invasion		R 3 C 1	P 1		P 2 C 1	C 1	P 3 R 3 C 3
Total	0	4	1	0	3	1	9
Total	15	21	9	1	3	1	50
		34					

*P: punch, R: ring, C: cone, A: amputation.

While we feel less timid than formerly about treating carcinoma in situ in properly selected instances by conservative measures which will preserve the childbearing function, we wish to emphasize that this method is considered only when conditions are such as to permit frequent cytological follow-up of these cases. We would stress also that, except for those occasional cases where conservatism seems advisable, we, as in most clinics, still prefer hysterectomy for the average case of carcinoma in situ (Table V). Of our 50 cases, 34 were

so treated, 4 with radical hysterectomies and pelvic lymphadenectomies (none had positive nodes), and one other was treated with x-ray and radium. Here, again, we feel that the extensive biopsy specimen has proved to be most advantageous in planning the extent of the hysterectomy. In limited intraepithelial lesions, the usual complete hysterectomy should suffice, but one should excise enough vagina to be well away from the vaginal portion of the cervix. If indicated, the adnexa may be preserved. In instances where the lesion has involved the cervical glands extensively we prefer a wider excision in the region of the cervix, and if there is any question of early invasion we have done a more radical hysterectomy with a pelvic lymphadenectomy.

Conclusions

In our experience with the treatment of 50 cases of carcinoma in situ of the cervix, 15 patients have remained cytologically negative for from 6 months to over 2½ years after having had no other procedure than an extensive cervical biopsy excision; 34 have had hysterectomies (4 with pelvic lymphadenectomies); and 1 was treated with x-ray and radium. In 25 cases, extensive biopsy excision of the cervix had preceded the hysterectomy, and in 21 of these no residual disease could be found in the hysterectomy specimen. The 4 cases with residual disease continued to have positive cytology smears after the biopsy procedure and preceding the hysterectomy.

Experience gained from this study indicates that, when desirable, conservative treatment of carcinoma in situ may be carried out, provided that a sufficiently large area of cervical tissue is removed by cone excision or partial amputation, and provided that the case is closely followed by cytological smear examinations.

We wish to be the first to note that 50 cases is not a large series from which to draw sweeping conclusions, and that the study groups are too small to be significant statistically. The information derived from this analysis, however, has helped us in treating these cases, and we hope, therefore, justifies our presenting them to you.

We wish to acknowledge the valuable assistance of Miss Edith Baker, Head of the Medical Art Laboratory, Roosevelt Hospital.

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Discussion

DR. HOWARD C. TAYLOR, JR., New York, N. Y.—Dr. Peightal and his co-workers have performed an important service in the collection and examination of the large amount of material from The Roosevelt Hospital and in the presentation of the case for the conservative handling of at least certain cases of carcinoma in situ. What comments I have to make are not criticisms of Dr. Peightal's paper in particular, but concern the uncertainties which surround this subject in general. I should like to comment first upon the question of incidence and then on the safety of conservative treatment.

In Dr. Peightal's series of 5,847 patients examined by cytologic methods there were 71 positive smears, from which 14 cases were subtracted on account of incomplete data and 7 more because subsequent biopsy showed only "anaplasia short of carcinoma in situ." This gives an incidence of about 1 per cent. From our own clinic Gusberg has reported an incidence of 1.6 per cent, and some frequencies of more than 2 per cent have been noted. All of these figures represent an incidence higher than theoretical calculations would lead us to expect.

The expected frequency may be reached somewhat as follows: Since carcinoma in situ has an average life history of five years before it reaches a clinical stage, it might be possible to detect such a case at any examination during the five years preceding the first symptom. The incidence of carcinoma in situ should, therefore, be no higher than five times that of the annual incidence of new cases of clinical cancer. If this reasoning is correct, the expected frequency of carcinoma in situ should be about 0.3 per cent. This is approximately the figure being reported by the Strang Clinic at the Memorial Hospital in New York.

The question of incidence is important in evaluating success in therapy. A high incidence of carcinoma in situ in a given series may mean one of two things. In the first place, the series may not be an unselected one. In the second place, cases may have been included by the pathologist that were never destined to become carcinoma. If the latter is the explanation, then the reason for the success of therapy by the coning biopsy becomes apparent.

With our present state of knowledge, I think that the general opinion would support Dr. Peightal in his conservative therapy of women in their twenties and thirties. His great care in the management of these cases, beginning with "a wide ring, a deep cone, or a partial amputation of the cervix" and followed by cytologic tests every one to four months should be noted. It would be interesting to hear whether his conservatism in the treatment of these 15 cases has resulted in any successful pregnancies.

Yet it must not be forgotten that the conservative treatment of carcinoma in situ does constitute a risk, if a small one. Dr. Peightal himself notes that in 4 of 25 specimens obtained by hysterectomy after extensive biopsy procedures, residual disease was present. It must be remembered also that these 4 failures to eradicate the disease by coning biopsy occurred in the hands of skilled operators who had their minds concentrated on this problem.

No instances of the development of invasive carcinoma or death of the patient following a coning biopsy for intraepithelial carcinoma of the cervix are known to me. It would be interesting to know if any members of this audience can report any.

The development of true carcinoma and one or two deaths from cancer in a series of cases of carcinoma in situ deliberately untreated was described in this country by a visitor from abroad two years ago. This observation has apparently not appeared in print. In our own clinic we have had the experience of observing a patient with what was supposed to be carcinoma in situ throughout most of her pregnancy without therapy. A positive Papanicolaou test obtained at the fourth month was followed by a series of equivocal biopsies. Although under the circumstances it was not possible to prove the absence of invasion, the suggestion of active therapy was not pressed on account of the patient's religious convictions. A biopsy taken at delivery showed an early invasive lesion of the anterior lip, and in spite of radiation therapy she died of recurrences at the end of two years.

This was probably a very special case, where circumstances prevented the complete tissue examination that Dr. Peightal was able to carry out. Nevertheless, it serves to remind one that this may be a potentially fatal lesion and that it must be handled with the greatest possible care.

DR. FRANK L. McPHAIL, Great Falls, Mont.—We have been following a plan of study similar to Dr. Peightal's. I am able to add 14 cases which fit the criteria he has established.

The cases shown in Table I were originally detected by Papanicolaou smears. The punch biopsy tabulated is the last of that series. The four-quadrant technique had previously been used but residual carcinoma in situ was found to be present in all cases. The circle biopsies removed the entire squamocolumnar junction, but this method also has been discontinued for the same reason.

Four patients had amputation biopsies. The one patient in this group whose biopsy was followed by a hysterectomy was found to have carcinoma in situ at the level of the amputation biopsy. Conization biopsies were performed in 6 cases. Residual carcinoma in situ was found in one case only. Three cases were treated by amputation biopsy alone. Frequent cytopathologic studies have been carried out on these 3 patients. One patient has been followed for four years, one for two years, and one for only one year. The smears have remained negative to date.

TABLE I. CORRELATION OF BIOPSY METHOD AND TREATMENT

		TREATMENT		
			HYSTERECTOMY	
TYPE OF BIOPSY	NUMBER OF CASES	BIOPSY ONLY	NO RESIDUAL	RESIDUAL
Punch biopsy	1			1
Circle biopsy	3			3
Amputation	4	3		1
Conization biopsy	6		5	1
			5	6
Total	14	3	11	

Dr. Peightal has called attention to some very important facts in this paper, on the basis of which there are some points which cannot be ignored:

1. A biopsy of the entire cervix must be made. A single biopsy diagnosed carcinoma in situ and not augmented by a total biopsy has been proved to be inadequate.

2. The total biopsy must be studied throughout its entire extent. Both multiple sections and serial sections of questionable areas are necessary. This requires an intimate knowledge of the pathologic methods employed, if the question of invasive carcinoma is to be excluded.

3. If treatment of carcinoma in situ by either emputation or conization is elected, the follow-up studies must be painstaking. Cytopathologic studies must be frequent, and the slides must be studied by competent observers.

If each biopsy is studied completely, and if follow-up observation is accomplished by well-trained technicians and pathologists, it should be possible to follow selected patients without always resorting to radical treatment.

The nature of carcinoma in situ is still controversial. Novak has remarked that the lesion does not need to be treated with the same speed as a perforated gastric ulcer. Certainly conservation of the power of reproduction is a worth-while objective, provided that conservation is safe. By a study of collected experiences such as these reported by Dr. Peightal, we may evaluate the safety of watching these patients through careful examination and frequent study of vaginal and cervical smears.

DR. WILLIAM B. THOMPSON, Hollywood, Calif.—Some eight years ago, a residency in obstetrics was established at the Hollywood Presbyterian Hospital. Since there was only a small clinic and not enough work to keep a resident interested, my associate, Dr. Emil Krahulik, and I suggested that the resident begin a histologic study of the cervix at term. Such a study was possible because several of us had been doing routine cervical repairs at the time of delivery, and the bits of trimmings from that procedure were available. Dr. Maurice V. Sheets, the first resident, reported in 1950 the results of 200 cervical studies, and now has extended the total to 1,300. It should be noted that in all cases the material obtained is from the sites of lacerations, usually at the lateral borders of the cervix. Rarely was tissue removed from either the anterior or the posterior surface.

When this study was begun, Dr. Sheets became enthusiastic over the possibility of discovering early carcinoma. I assured him that he never would do so, and that it would not be necessary to use a microscope to detect cervical carcinoma associated with pregnancy. The fourteenth cervix studied, however, showed a highly suggestive area (Fig. 1). The sections were sent to several excellent gynecologic pathologists, and all agreed that they represented early invasive carcinoma. I was much concerned, since this was my patient. After some debate, a total hysterectomy was done, and the entire cervix sectioned.

Fig. 1.

Fig. 2.

Fig. 1.—Early invasive carcinoma shown at the time of delivery.
Fig. 2.—Invasive carcinoma removed six months post partum.

In only one of sixteen blocks was there any disturbance of architecture (Fig. 2), consisting of some extension into glands and a small area of stromal invasion. I have seen this patient within the past month, and can report that there is no evidence of recurrence in the vaginal vault, and that the pelvis seems to be perfectly normal.

The one hundred eighty-second patient was one of Dr. Krahulik's. Again early invasion was noted (Fig. 3), rather more definite than with my patient. This woman refused hysterectomy, however, and shortly thereafter moved to New York. We have not been able to get in contact with her, and hence cannot report on the possible progress of the lesion. Incidentally, these are the only two instances of invasive growths in the series, and it is ironical that they should be patients of the two who suggested and supported the study.

Fig. 3.—Early invasive carcinoma shown at the time of delivery.

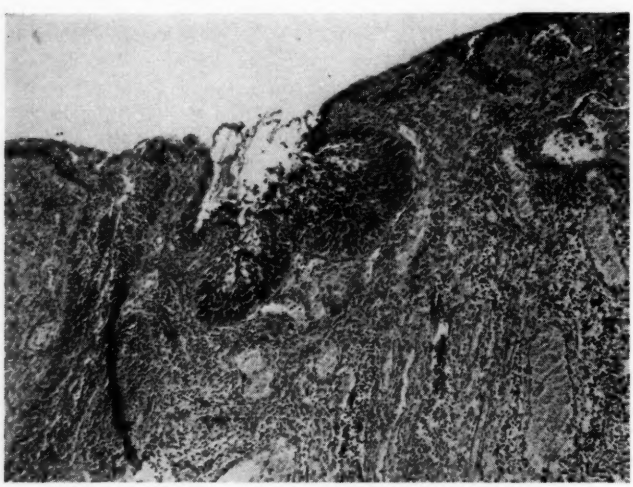

Fig. 4.—Carcinoma in situ at the time of delivery.

There were 4 cases in which the histologic studies revealed possible carcinoma in situ. One of these was a tangential cut, and further study of correctly cut sections disproved the earlier impression of malignancy. One of the three remaining cases was again a patient of mine (Fig. 4), although inadvertently the findings were not reported to me until about six weeks ago. It took some time to locate her, and not until ten days ago did I get her into the office for smear studies. The cervix was smooth and free of erosions or eversions. Smears were sent to two laboratories. One reported negative findings, but

Dr. Daniel G. Morton's technician reported finding cells of a malignant type—evidence that if one hopes to treat these lesions conservatively, one must be sure that the smears are read by competently trained persons. This patient will soon undergo operative treatment.

Thirteen hundred cervical sections taken at delivery constitute a fairly broad sample, and the fact that the cases were unselected would lead one to expect a low incidence of associated abnormalities. In 82 (6.3 per cent), however, the sections showed some degree of disturbance in the architecture of the basal elements. Whether these disturbances indicate that, in later life, increased changes will eventually lead to carcinoma is something that cannot be foretold. To date no follow-up of these cases has been attempted. Only 13 of the 82 have been examined by smear, and all smears were reported negative. It seems to me, however, that these patients should be followed over a long period—twenty or thirty years—before one could state whether changes in the basal structure during pregnancy are as significant as changes occurring in the nonpregnant cervix.

DR. RICHARD BRYANT, Cincinnati, Ohio.—Dr. Taylor's case reminded me of one we had, which demonstrates some of the pitfalls in the management of this condition.

We had a patient, four months pregnant, whose routine smear demonstrated some abnormal cells. Four quadrant punch biopsies were done which revealed questionable carcinoma in situ. We repeated the biopsies, with similar results. We finally decided that it probably was carcinoma in situ, and the patient was allowed to go on with her pregnancy. She went into labor spontaneously, and late in the first stage of labor the uterus ruptured. The abdomen was opened and a hysterectomy was done. Infiltrating the base of the right broad ligament was frank carcinoma, so extensive that nothing more than a simple hysterectomy could be done at that time. The patient was treated subsequently, of course, but has died of her carcinoma.

The interesting points to me are that the biopsies indicated a questionable carcinoma in situ, whereas actually the patient had very extensive invasive carcinoma. Several questions are raised: Whether the so-called carcinoma in situ was an entirely different lesion from the actual carcinoma, or whether it was a lesion merely at the perimeter of the actual carcinoma. This case demonstrated to us a point which I am sure is implied in the speaker's paper—that among other things which should be done when you are searching for carcinoma in situ is an adequate pelvic examination. Carcinoma in situ does not rule out carcinoma.

DR. PEIGHTAL (Closing).—Dr. Taylor has noted some contradictions between our reported incidence and those to be expected from the reported general incidence of cervix carcinoma. This variance is to be expected, for the 5,847 patients studied were not an average sample of the population. Seventy per cent were private, 30 per cent clinic patients, and in the great majority of the private cases smears were taken only if the history or clinical findings indicated the need for cytologic study.

Dr. McPhail has added a group of cases carefully studied postoperatively after various biopsy procedures, and it is noteworthy that he too has found no residual disease in a proportion of cases following either amputation or deep cone biopsies. Similarly Dr. Thompson's report of tissue samplings from more than 1,300 cases adds much to our knowledge of the incidence of carcinoma in situ and gives us the benefit of his observation of several of these cases over seven years without recurrence.

We would again emphasize, in closing, that conservative treatment of carcinoma in situ is justified only if the biopsy cone or amputation is of sufficient proportions to rule out invasive cancer, and if the case is then followed regularly by cytologic smears. Furthermore, we feel that conservative treatment should be reserved for those patients whose age and marital state justify it, and that otherwise hysterectomy is the treatment of choice for this lesion.

NONINVOLUTION OF THE PLACENTAL SITE: CLINICAL AND PATHOLOGICAL STUDIES*

HAROLD L. GAINEY, M.D., KENNETH S. NICOLAY, M.D., AND ANGELO LAPI, M.D., KANSAS CITY, MO.

HEMORRHAGE, which continues to be a hazard for the obstetrical patient, requires knowledge of the underlying pathology on the part of the attendant for its successful management. Antepartum and intrapartum hemorrhage, to the well-informed obstetrician, seems well categorized, particularly since the work of Fish and associates,[1] defining rupture of the marginal sinus clinically, and in view of the increasing emphasis on the importance of circumvallate placenta with its attendant dangers. The now apparent overemphasis on placenta previa and abruptio placentae is being re-evaluated. Hemorrhage associated with the third stage and its management has shown marked improvement following the recommendations of Davis and Boynton,[2] and Dieckmann and co-workers.[3]

Hemorrhage in the puerperium, frequently discussed under the appellation of "late postpartum hemorrhage" or "delayed postpartum bleeding," is one of the most distressing complications for patients, and it is difficult to manage from the attendant's standpoint. Various writers state that the time of occurrence of the bleeding, falling into this classification, is from a minimum of twenty-four hours to fourteen days. Our belief is that in many instances the same factors are present from a few hours to as much as six weeks or more post partum, noninvolution of the placental site and retained placental fragments being responsible.

Excluding neoplasms, rupture of varicosities, uterine inversion, and so forth, alterations in normal uterine physiology related to pregnancy and the puerperium as causes for delayed postpartum bleeding are variously listed as retained placental tissue, noninvolution of the placental site,[3, 4, 5] deciduoma,[6] and syncytial endometritis.

A renewed emphasis upon noninvolution of the placental site has been chosen as the subject of this presentation. The reason for its selection is that it has superseded all other etiological factors as to frequency of incidence and gravity of consequences. In a review of 5,429 deliveries, 24 patients had postpartum bleeding severe enough to require active therapy (curettage) while still hospitalized or re-admission to the hospital for treatment. Of these, 5 had retained secundines, 10 had no significant findings and probably could have been managed conservatively, and 7 presented the clinical picture under discussion. Two additional patients were curetted within 8 hours of delivery. These cases will be discussed briefly. An evaluation of the literature reviewed was impos-

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

sible, but the impression was gained that this entity far outnumbered any other indication for hysterectomy for delayed postpartum bleeding. As yet, we have not had to resort to hysterectomy in the management of these patients; an additional case which required hysterectomy, however, obtained from another source, will be presented (Case 6).

The physiology of the involution of the placental site has been described by Goodall,[7] Teacher,[8] and J. W. Williams.[9] Williams, in 1931, showed that necrosis of any retained decidua is complete by the seventh postpartum day, and that the subsequent detachment of the decidual slough is completed by the twelfth day. At this time, the raw surface of the uterus is relined by cells proceeding from the fundi of the glands. By the twenty-first postpartum day, the uterine endometrium has been completely regenerated except at the placental site. Abnormalities of decidual involution and separation are factors in late postpartum hemorrhage but to a mild degree and probably represent those that respond to diethylstilbestrol.

Involution of the placental site is a totally different process.[7, 8, 9] Immediate hemostasis following delivery of the placenta is effected by contraction of the uterus compressing the blood vessels. This is maintained by retraction of the muscle bundles, with clotting and thrombosis in the blood vessels. The foregoing immediate processes are followed by the sequential events in the arteries and veins described by Goodall[7] in 1909. The fibrous tissue of the media and adventitia undergo hyaline degeneration, the elastica interna becoming swollen and degenerated. The hyalin of the muscle coat then invades the elastica interna and the vessel lumen, replacing the blood clot. The ultimate result is obliteration of the lumen by a hyaline substance. Recanalization completes the process.

In the veins, which have no definite elastica interna, all the walls contain elastic fibers intermingled with fibrous tissue. In the postpartum period the fibrous tissue swells and becomes hyalinized, thus reducing the lumen of the vein which is filled with clot. In normal involution the hyalin in the vein wall is later reconverted into elastic tissue.

Epithelization of the placental site by the endometrium, described by Williams,[9] is completed about the sixth week by an undermining process that extrudes the vessels of the placental site which protrude polyp-like from the surface. Normal involution will accomplish this end by six weeks.

According to Rutherford and Hertig,[5] persistent noninvolution of the placental site has been reported as late as nine weeks. Local and systemic infections and debilitating diseases do not seem to alter the schedule of involution of the placental site.[8] Myometrial involution is delayed by these factors.

The pathogenesis of this grave puerperal complication is at present conjectural. Any explanation is, of necessity, based upon altered physiology rather than associated pathology. There were no instances of uterine anomaly, submucous myoma, or puerperal infection. One case showed adenomyosis uteri. Although faulty separation with manual removal of placenta has been reported preceding this complication, an abnormal placental stage was not associated in our experience. The physiology of the puerperium was not altered by oxy-

tocics or endocrine preparations, with the exception of Patient 5, who received stilbestrol to suppress lactation. Early ambulation was the rule in all cases. All patients were multiparous, with normal past histories.

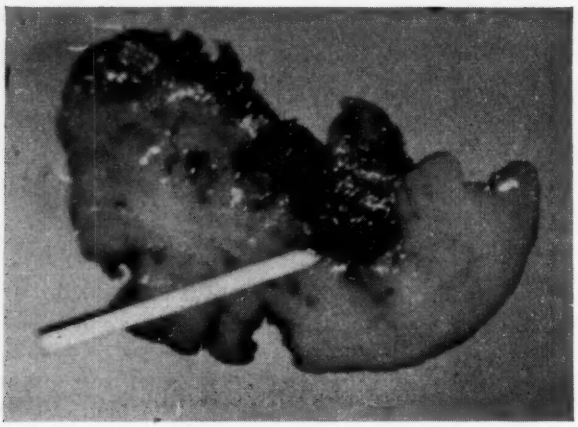

Fig. 1.—Section of uterus, showing placental site.

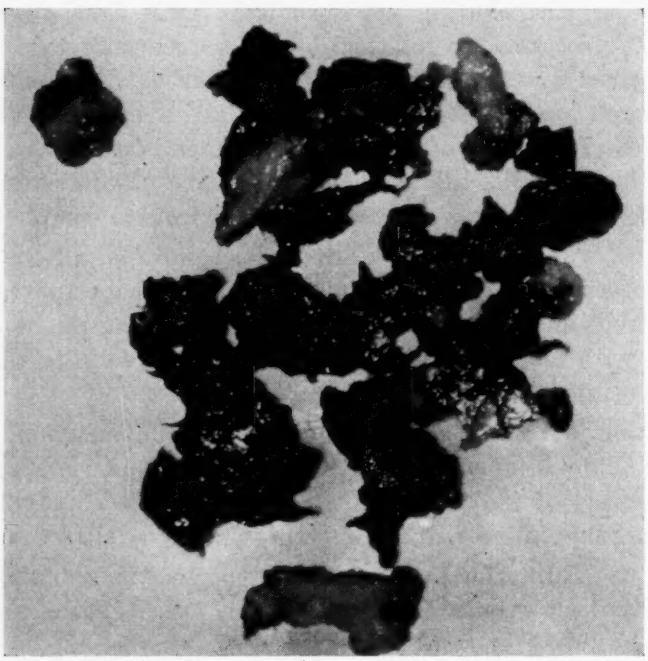

Fig. 2.—Curettings from placental site.

The cases of postpartum bleeding which occurred from a few hours to two weeks post partum were associated with rather constant clinical physical findings. The cervix was patulous, the uterus large (the size of a twelve to fourteen weeks' gestation), with thin walls and filled with old blood clots undergoing autolysis or fibrinolysis. These findings were like those described in the literature by Melody,[10] Rutherford and Hertig,[5] Wolfe,[4] and N. H. Williams.[6] The placental site was estimated to be 6 to 10 cm. in diameter and 0.5 to 1 cm. in

elevation, covered with firmly adherent blood clots suggesting organization like that of granulation tisue (Fig. 1). For a time the term "granuloma of the placental site" was applied, but histologic studies did not bear this out. Each

Fig. 3.

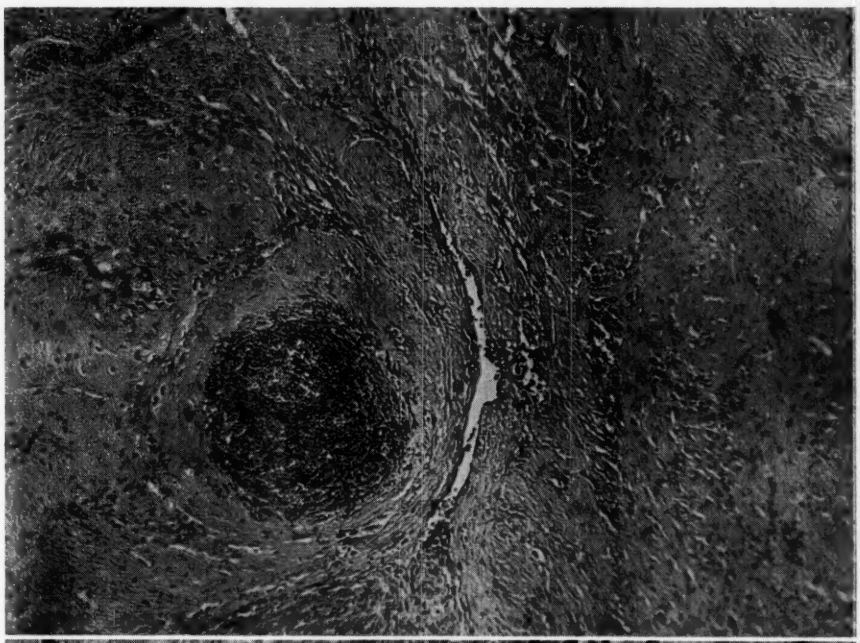

Fig. 4.

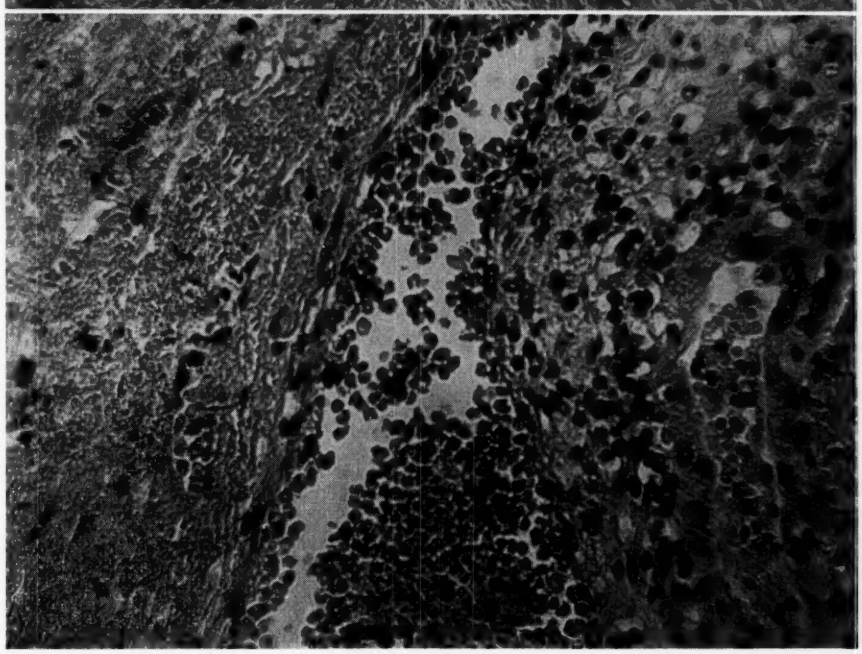

Fig. 3.—An early organizing thrombus in a vessel, showing moderate hyaline degeneration of media. Surrounding tissue is myometrium.

Fig. 4.—Recanalization of thrombus, showing endothelium-lined space at the margin containing fresh blood.

placental site was normal in location. At the time of curettage, 20 to 50 Gm. of firm, rubbery, amorphous material which was firmly "adherent" to the placental site was obtained (Fig. 2).

Histologically, the following features were common to all curettings from placental sites which were studied: (1) myometrial tissue, (2) large, thick-walled blood vessels showing varying degrees of hyaline degeneration, (3) organizing thrombi within the lumina (Fig. 3), (4) endothelium-lined spaces filled with blood or organizing thrombi, (5) frequent instances of recanalization of thrombi (Fig. 4). Syncytial giant cells could not be demonstrated with assurance. Placental tissue was absent, and inflammatory cellular infiltration was limited to necrotic fragments and was minimal.

Case Reports

CASE 1.—(S.M.H. 206374) Mrs. K. M., 30 years of age, gravida iii, para ii, was admitted to St. Mary's Hospital on the two hundred eighty-third day of gestation. Her past history was negative. Labor was uneventful, with spontaneous delivery. The placenta was delivered spontaneously. Total blood loss was 50 c.c. No oxytocic was given. The postpartum course was uneventful until the fifth day, at which time lochia serosa was noted. On the sixth day there was a small amount of bright red bleeding and she had saturated six vulvar pads during the preceding night. At 7:15 A.M., there was a large amount of bright red bleeding.

The patient was taken to surgery at 8:00 A.M., on the sixth postpartum day. Examination under anesthesia revealed the uterus to be the size of a twelve to fourteen weeks' gestation, filled with clots. On the right anterior aspect of the endometrial cavity, there was an area about 8 cm. in diameter which was rough, granular, and slightly elevated. This was curetted digitally and tissue of a granulomatous nature was obtained. The uterus was then curetted with a sharp curette. Following this a uterine pack was inserted. The patient received four transfusions during and after surgery. Hemoglobin prior to the onset of bleeding was 82 per cent.

Mild shock with blood pressure as low as 70/50 occurred postoperatively. The patient bled through the pack and was given Ergotrate, 1/320 grain, every four hours. Seven hours following the curettement, she had a chill, became cyanotic, and the temperature rose to 101.8° F. Following the chill, penicillin and streptomycin were started. By the following morning, the temperature was normal, and remained normal thereafter. Twenty-four hours following surgery the pack was removed and there was no unusual bleeding. The patient was asymptomatic thereafter. She was kept on Ergotrate, antibiotics, and stilbestrol for five days, and dismissed on the fifteenth postpartum day. At the time of dismissal, following four transfusions, the hemoglobin was 62 per cent.

Pathological Report.—There were many large blood vessels in the myometrium, some of which were filled with organized thrombi, frequently showing recanalization. Many of the blood vessels showed advanced hyaline degeneration of the wall. Thrombi occasionally formed part of the endometrial surface. There was slight to moderate necrosis of some of the surface tissue, and a few infiltrating neutrophils were seen in these areas. There was no placental tissue.

CASE 2.—(S.L.H. 53-5454) Mrs. J. B., 25 years of age, gravida ii, para i, was admitted to St. Luke's Hospital on the two hundred seventy-eighth day of gestation. Labor and delivery were uneventful. Ergotrate was given following the third stage. Total blood loss was 100 c.c. The third and fourth postpartum days were uneventful. Bleeding was described as normal. On the morning of the sixth postpartum day, the bleeding increased, becoming severe.

On examination under anesthesia, the cervix was found to be patulous. The uterus was enlarged to about the size of a twelve to sixteen weeks' gestation, thin walled, and

filled with clots. A finger was inserted in the endometrial cavity. At the fundus of the uterus, extending partially both anteriorly and posteriorly and a little more to the left, a large, rough, elevated area was encountered. Digital curettage showed that it was markedly adherent even to the extent of suggesting the possibility of placenta accreta. After prolonged attempts with sponge forceps, digital curettage, and light, sharp curettage, a large amount of tissue was obtained which had the appearance of decidua, placenta, and myometrium. The uterus was packed, requiring about 8 yards of 2 inch uterine packing. A postoperative diagnosis was deferred for the histological report, which showed no placental tissue. There were still areas of adherent, irregular, granular tissue left in the uterus. The patient received one transfusion during surgery and one following. Penicillin was given prophylactically. The pack was removed 24 hours later, and bleeding was normal thereafter. The hemoglobin was 78 per cent, with 3.94 million red blood cells on dismissal from the hospital on the tenth postpartum day.

Pathological Report.—There was much necrosis near the surface, and the necrotic area was heavily infiltrated with neutrophils. There was no placental tissue. Large blood vessels filled with thrombi showing early organization were seen near the surface. The walls of the vessels showed well-advanced hyaline degeneration with complete hyaline occlusion of some of the vessels. Occasionally a small central lumen in some of the thick-walled vessels was occluded by an organizing thrombus. Many of the larger blood vessels were tortuous. A considerable number of empty or blood-filled vascular spaces lined by endothelium and without demonstrable walls were seen throughout the myometrium. Often these spaces were collapsed. Decidual tissue was scanty, and frequently contained a few collapsed glands lined by flattened or low cuboidal epithelium.

CASE 3.—(S.M.H. 233004) Mrs. R. W. was 30 years old, gravida iii, para ii. Her prenatal course was uneventful. She was admitted to St. Mary's Hospital on the two hundred ninety-second day of gestation. Labor and delivery were uneventful. The postpartum course was entirely without incident, and she was dismissed on the sixth postpartum day. Twenty-four hours following dismissal from the hospital, vaginal bleeding became excessive and when the patient was first seen the uterus was enlarged to two-thirds of the way to the umbilicus, quite soft, atonic, and contained many clots. She was admitted to the hospital. A transfusion of 500 c.c. of whole blood was administered to compensate for blood already lost. Laboratory reports revealed normal clotting, bleeding, and prothrombin times. Intravenous Ergotrate was given. Following expulsion of the old clots, bleeding became minimal.

The patient was taken to the operating room and the uterus was found to be the size of a twelve weeks' gestation. The cervix was patulous and admitted two fingers easily. The placental site was identified by a raised, roughened area in the uterine fundus, extending approximately one third of the way down the anterior and posterior walls of the uterus. With the fingers, adherent clot and tissue, grossly resembling placental tissue, were removed from the placental site, followed by curettage with the sharp curette by which additional tissue was obtained. Because of continued bleeding, the uterus was packed. The pack was removed eighteen hours following the curettement. Antibiotics were administered prophylactically. The postoperative course was afebrile. The patient was dismissed from the hospital on the fifth postoperative day. The hemoglobin was 72 per cent. The pathological report was placental site consistent with the immediate postpartum period. Multiple sections failed to show any placental tissue.

Pathological Report.—The material was made up largely of myometrium in which were many large blood vessels with thick hyaline walls, sometimes containing thrombi within the lumen. Many of the larger vessels were completely obliterated as a result of hyaline degeneration and resembled corpora albicantia. Also noted were many endothelium-lined spaces filled with thrombi in which were recanalizations. There was no placental tissue nor inflammatory cellular exudate.

CASE 4.—(S.L.H. 52-4231) Mrs. N. A., 36 years of age, gravida iv, para iii, was admitted to St. Luke's Hospital on the two hundred seventy-second day of gestation.

Labor and delivery were uneventful. Ergotrate, 1/320 grain, was given with crowning. The placenta was delivered by simple expression. The postpartum course was uneventful with dismissal on the seventh postpartum day. There were no unusual bleeding and no morbidity. The patient was readmitted on the eleventh postpartum day. Bleeding was profuse, and there were signs of shock with a blood pressure of 70/0 and rapid pulse. At the time she was admitted to the hospital the blood pressure had risen to 130/70, and the temperature was 100.4° F.

In the operating room, the uterus was found to be the size of a twelve to fourteen weeks' gestation. The cervix was patulous, admitting four fingers. The endometrial cavity was distended with old and recent blood clots, estimated to be 1,000 c.c. The myometrium was 0.5 to 1 cm. in thickness. An elevated area, 6 cm. in diameter, on the anterior wall of the uterine cavity was identified as the placental site. This was curetted digitally and about 30 Gm. of firm rubbery material obtained. No placental tissue was recognizable. The uterus was packed. Pituitrin, 1 c.c., was administered intramuscularly during operation. Four transfusions were given during and after operation. Penicillin, sulfadiazine, and Ergotrate were given in the postoperative course. The highest temperature recorded was 101.4° F. the evening following surgery. The pack was removed the following morning and again that day she ran a temperature of 101.2°. Three days following surgery, Ergotrate was discontinued and the remainder of the postoperative course was uncomplicated. The hemoglobin was 56 per cent and the erythrocyte count 2.61 million after three blood transfusions. A fourth transfusion was administered. She was dismissed on the fifth postoperative day and her course was uneventful thereafter.

Pathological Report.—Many large, thick-walled blood vessels showing hyaline degeneration of the walls were scattered throughout the myometrium. In the lumina of some of the vessels were organizing thrombi. There was no placental tissue, and inflammatory cellular exudate was limited to a few infiltrating chronic inflammatory cells near the surface. The myometrial fibers were pale and swollen and frequently without demonstrable nuclei.

CASE 5.—(S.L.H. 125837) Mrs. A. S., aged 35 years, gravida iv, para ii, was admitted to St. Luke's Hospital in labor on the two hundred fifty-eighth day of gestation with a diagnosis of intrauterine death of the fetus. The previous pregnancy had resulted in the delivery of an erythroblastotic infant. Following an uneventful labor and delivery, a stillborn infant was delivered. The placenta was delivered by simple expression. Infundin, 1 c.c., was given prior to its delivery and Ergotrate, 1/320 grain, afterward. The total blood loss was 600 c.c. A transfusion of Rh-positive blood was given, and after 150 c.c. the patient had a severe chill. The temperature rose to 104° F. The transfusion was discontinued. The temperature returned to normal by the following morning. She received sulfadiazine for four days and stilbestrol, 5 mg. twice a day, for seven days. She was dismissed from the hospital on the seventh postpartum day.

Readmission took place eighteen days post partum because of excessive bleeding. The operative note describes the uterus as four times normal size. The cervical os easily admitted one finger. There was an area on the posterior wall of the uterus which was roughened, and from this area fragments of tissue were obtained with a curette. The uterus was packed. The packing was removed the following morning. Ergotrate was given every four hours for the next forty-eight hours.

The bleeding, however, continued to be excessive, and eight days later she was transfused with one unit of blood. Ten days after the first curettage, she was again taken to the operating room and curetted. There is no description of the operative findings at this time; however, the uterus was packed. The pack was removed the following morning. The temperature rose to 103° F. and fell gradually by lysis over the following seventy-two hours and by the fourth postoperative day was normal. During this time the patient was placed on sulfadiazine, 1 Gm. every four hours, for four days. She was placed on penicillin, 30,000 units every three hours, which was continued until the end of her hospital stay thirty days later. She was transfused on the first and third postoperative days and

again on the twentieth, making a total of three transfusions. The hemoglobin was 52 per cent with 3 million red blood cells. On the twelfth day following the last curettement, she again became morbid, the temperature rising to 102° to 104° F. This course continued for the following thirteen days. A diagnosis of septic thrombophlebitis with pulmonary emboli was made. Penicillin was increased to 50,000 units every three hours. The temperature began to improve slowly and it was normal and remained so until the time of her discharge three weeks later. At the time of her dismissal from the hospital, the hemoglobin was 62 per cent, with 3 million red blood cells. She received one more transfusion, a total of four.

Pathological Report.—There were many thick-walled blood vessels filled with organizing thrombi. The walls of the vessels showed different degrees of hyaline degeration, frequently with complete obliteration of the lumen. Many large blood vessels were closely grouped, superficially resembling a cavernous hemangioma. The vessels were separated by a loose or dense collagenous connective tissue in which were a few infiltrating chronic inflammatory cells. A few small necrotic areas were noted. There was no placental tissue.

CASE 6.—(Mercy Hosp., San Diego, Calif., 268572) The patient was a 38-year-old white woman, gravida iii, para ii. Labor and delivery were uneventful. The placenta was delivered intact and there was minimal bleeding in the immediate postpartum period. The hospital course was essentially normal. It was noted that the patient's lochia was very scant. She was discharged on the third postpartum day. At the time of discharge the hemoglobin was 51 per cent, with 2.57 million red blood cells. The patient was given iron therapy at the time she was dismissed. The course at home was normal until the seventh postpartum day. At 10:00 A.M., there was sudden, profuse vaginal bleeding which was estimated at 500 c.c. The patient was admitted to Mercy Hospital at 1:30 P.M. At that time the uterus was firm and there was a moderate amount of bleeding. At 3:00 P.M. the bleeding became more profuse and the uterus seemed to be less firm.

At 5:05 P.M. the patient was taken to the operating room. The pelvic examination was as follows: The vagina was filled with fresh, bright red blood. The cervix was dilated 3 to 4 cm., and the uterus was the size of an eight to ten weeks' pregnancy. The uterus was explored with 2 fingers in the cervix and suprafundal pressure. A roughtened area was found in the region of the right cornu which seemed to be raised above the surface about 1 cm. Several firm, necrotic pieces of tissue were removed. The site was reexamined and still found to be shaggy to palpation. Several more pieces were then removed with ring forceps, but bleeding continued. An attempt was made to curette the site gently with a sharp curette, but this increased the amount of bleeding. The uterus was then packed with a 2 inch pack, and Ergotrate was given intravenously. The bleeding seemed to be controlled for short intervals, and then began soaking through the pack. The packs were removed. The uterus was repacked, but bleeding continued. It was felt at this time that, because of the excessive blood loss and uncontrollable hemorrhage, a hysterectomy was indicated.

The abdomen was opened through a midline incision. There was no blood in the peritoneal cavity and the uterus was intact. In view of the patient's excessive blood loss and prolonged shock, a subtotal hysterectomy was done, because of the shorter time involved. She was given a total of 8 pints of blood during the operative procedure and immediately following it. Her immediate postoperative condition was fair. The postoperative course was relatively uneventful with the exception of pyelitis, which responded to medication. She was discharged on the eleventh postoperative day in good condition.

Pathological Report.—The material consisted essentially of myometrium in which were scattered islands of endometrial tissue, including glands and stroma. The stroma showed marked decidual reaction. Near one surface were large endothelium-lined vascular spaces which were usually filled with partly organizing thrombi. There were also many interstitial hemorrhages. Some of the thrombi formed part of the surface as described by Williams.[9] The organizing thrombi frequently merged imperceptibly with the walls of the

vessels showing varying degrees of hyaline degeneration. An endometrium as such could not be recognized, but fragments of columnar epithelium and a few scattered atypical glands lined by simple columnar epithelium were seen near the surface. Many of the blood vessels showed a definite wall which varied in thickness and which showed different degrees of hyaline degeneration, sometimes with complete obliteration of the lumen. Other vascular spaces were lined only by endothelium and showed no definite wall. The myometrial fibers were hypertrophied and characterized by a pale, abundant cytoplasm. The nuclei of the myometrial fibers were considerably more vesicular and showed more prominent nucleoli than the muscle fibers of the media of blood vessels. The Weigert-van Gieson's stain showed a thin layer of connective tissue beneath the endothelium or at the periphery of the wall of the blood vessel, depending upon whether the channels were blood vessels or simply vascular spaces. This demarcation was not readily apparent in sections stained by hematoxylin. A few neutrophils and chronic inflammatory cells were seen in the areas of adenomyosis, but elsewhere no appreciable inflammatory cellular exudate could be seen. There was no placental tissue demonstrable. A small amount of recently clotted blood was noted on the surface. What appeared to be septa growing from the walls of the vessels into the organizing clot in the lumen probably represented the wall of the blood vessel duplicated upon itself because of extreme tortuosity of the vessels. There were, however, endothelium-lined spaces within some of the clots, representing areas of recanalization.

Comment

A pathogenesis for this clinical entity suggested itself as these cases were reviewed chronologically. Two patients with postpartum hemorrhage occurring in the first twenty-four hours were available for comparison with seven patients in whom bleeding occurred from six to eighteen days post partum. Added significance was assigned to these two, as they represented the only patients in 5,429 deliveries examined at this time in the puerperium with these findings.

These two patients—one following abruption of the placenta associated with Rh iso-immunization and fetal hydrops, and one gravida iv, para iv, with an uncomplicated course—were examined six to eight hours post partum because of moderately excessive bleeding. Each was found to have an atonic uterus filled with clots of "good retraction" adherent to the placental site by a characteristic fibrinous exudate. The placental sites were less well defined in the early hours than in two patients examined on the sixth postpartum day (Cases 1 and 2), and in one each on the seventh (Case 3) eleventh (Case 4), and eighteenth (Case 5) postpartum days. The only difference noted in the later cases was that the placental site was manifested by a greater degree of elevation and more densely adherent "thrombotic" structures.

Postpartum hemorrhage appears thus to be prevented immediately by an adequate clotting mechanism, the adherence of the clot to the placental site providing temporary hemostasis. Venous and arterial thrombosis completes the early mechanism of hemostasis.

The anomaly of involution which permits bleeding appears to be myometrial. The myometrium was found to be only 0.5 to 1.0 cm. in thickness in both the early and late cases, the normal being 3.0 to 5.0 cm.

The reported patency of the blood vessels at this time due to failure of the normal obliterative vascular changes described by Goodall,[7] permitting profuse

hemorrhage, was not evident and the histological changes in the vascular structures were similar to conditions noted in the normal.

The anomalous feature observed in these patients was the markedly distended, thin-walled uterus. This undoubtedly had been present for a period of time and possibly from a few hours post partum, as indicated by the appearance of the blood clots. This extremely distended, thin myometrium may be a factor not only altering the early processes of normal vascular involution at the placental site, but affecting the vascular supply throughout the uterus.

The normal postpartum vascular changes are such that, unless physiologic uterine tone reconstitutes the tortuosity of the uterine vessels, hemorrhage will occur. These histological changes in the vessels are not diffuse and continuous, but patchy and nodulelike, the channel being patent except when the tortuosity resulting from normal myometrial involution is in effect. An analogy may be drawn from descriptions of the faulty mechanism associated with failure of obliteration of the ductus arteriosus. A prolonged contraction of the dense musculature of this vessel is necessary to accomplish the obliterative endarteritis.[11]

When the diagnosis of noninvolution of the placental site has been suspected on the basis of the described findings, successful management depends upon the following: (1) adequate facilities for blood replacement; (2) preparation of operating room facilities for both vaginal examination and hysterectomy; (3) intrauterine exploration, manually, with evacuation of clots and débridement of the placental site (tamponage and intravenous oxytocics should follow the curettage); (4) in the event of failure to control bleeding, immediate hysterectomy. Opinions differ regarding the value of curettage from complete condemnation to acceptance. To date, however, it has been successful in our hands.

These patients, as a result of blood loss and shock, may develop the added serious complication of incoagulable blood.[12, 13, 14] Recommended laboratory studies to detect the nature of the defect must be employed and proper treatment instituted. Recent literature has covered this aspect adequately.

Summary and Conclusions

A review of a group of 7 patients with delayed postpartum hemorrhage due to "noninvolution of the placental site" has been presented. This represents an incidence of 1:775. An eighth case report was added from another source.*

There were no significant anatomical or antecedent contributory factors. Multiparity and early ambulation, common to each case, may or may not be significant. Conservative management was successful in each. A review of histological studies did not reveal changes that could be differentiated from the normal.

The pathogenesis of this striking clinical entity is not entirely clear. Myometrial atonia, depriving the vascular structure of conditions favoring localized obliterative changes, suggests itself as a possible factor.

*We wish to express our appreciation to Dr. John F. Wanless, San Diego, California, for permission to use one of his cases in the preparation of this paper.

The precise basis for the term "noninvolution of the placental site" was not revealed in this study, and its usage has been accepted only for simplification in reporting. Further studies are necessary.

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Discussion

DR. BENJAMIN TENNEY, Boston, Mass.—Dr. Gainey has thrown considerable light on the problem of postpartum bleeding. His cases are well studied and documented. The treatment and results have been good.

It is of interest that all his cases have occurred within three weeks post partum, and four of them within a week, before the patients left the hospital. Although the pathological reports gave little evidence of infection, the fact that 3 patients had a febrile reaction after curettage suggests the possibility of underlying infection. Certainly no relation to the type or method of delivery could be demonstrated. The similarity of the pathological findings in this series suggests a clinical entity.

The absence of placental tissue is of importance. Too frequently, tissue removed from the postpartum uterus is assumed, on gross inspection, to be placental fragments. Careful microscopic study should always be done.

Six cases were chosen from the obstetric service at the Boston City Hospital which clinically fitted Dr. Gainey's classification. Each of these had been readmitted to the hospital for postpartum bleeding. The uterus was thin walled, the size of an eight to twelve weeks' pregnancy, and had a patulous os. The patients were readmitted three to six weeks after delivery, and there had been no previous episodes of hemorrhage. I cannot explain the delayed onset of hemorrhage in relation to Dr. Gainey's series.

The 6 cases were all treated by curettage. In only one, placental tissue was found. This finding supports Dr. Gainey's premise that noninvolution of the uterus, or, specifically, the placental site, is a more common cause of postpartum bleeding than retained secundines. It could be possible that, even in the case with retained placenta, subinvolution was involved in the hemorrhage.

In the other 5 cases, the findings and pathological descriptions were quite similar to those in Dr. Gainey's series. No special examination of the placental site was made at the time of curettage. We have previously felt that the whole uterus was involved as a source of bleeding.

From this description, it appears that there is a clinical entity which can be classified as subinvolution of the placental site. These cases must be differentiated from the more common type of postpartum bleeding, in which there is no definite subinvolution. Patients of this latter type, in spite of well-involuted uteri, may have excessive bleeding three to six weeks post partum. They can be successfully treated with oxytocics and endocrines. A curettage is rarely indicated.

I agree with Dr. Gainey that all patients with hemorrhage and subinvolution should have a curettage. We prefer not to pack the uterus after curettage, and have seldom found this procedure necessary.

That noninvolution of the placental site is primarily due to uterine atony and subinvolution has been suggested by the author. With this theory I heartily agree. The cause of the subinvolution is not always apparent. Chronic low-grade infection is always a possibility, although there are undoubtedly other causes.

In view of the underlying physiology, it appears that the term "granuloma" of the placental site is one that should be discarded in favor of "noninvolution."

DR. WALTER L. THOMAS, Durham, N. C.—My discussion is concerned with the report of one case, and speculation upon a possible psychologic or emotional component of this disease. The origin of this postpartum complication impresses us as an alteration in the physiology of involution. Certainly the pathological findings are inconclusive and vary little from the normal.

This 30-year-old white married primigravida was admitted to the hospital on May 10, 1953, in the first stage of active labor. Her pregnancy was full term and had been uncomplicated. It was noted during the conduct of her prenatal course that she was a perfectionist. She brought a list of questions at each visit which took plenty of time to answer. She was labeled as a patient with chronic anxiety and tension state.

On admission her blood pressure was 154/96 and she had slight edema. Labor progressed slowly, but delivery of a normal healthy female infant was easily accomplished after a labor of 22 hours and 45 minutes by assisted breech delivery. An intact placenta was spontaneously delivered within four minutes. Blood loss was estimated at 250 c.c.

The patient's blood pressure promptly fell to normal limits, and there was no further elevation. She was discharged on the ninth postpartum day.

The patient was readmitted to the hospital on May 20, 1953, 18 hours after discharge. She gave a history of profuse and painless vaginal bleeding of one hour's duration. The blood pressure was 80/40, the hemoglobin 65 per cent, with 3.2 million red blood cells. She was immediately placed on therapy to combat shock and taken to the operating room.

The uterus was found to be 3½ times the normal size, and boggy. The cervix was open, admitting three fingers, and there was very profuse bleeding. One cubic centimeter of Pitocin was given intravenously, and the uterine cavity was quickly explored with sponge forceps. Only clots were found. The uterus was then lightly curetted with a large, sharp curette, and only a minimal amount of tissue obtained; we saw nothing resembling placental fragments. The uterus and vagina were then tightly packed with 1 inch packing from the fundus to the introitus. The patient received a total of 1,000 c.c. of citrated blood.

Three-fourths of the uterovaginal tampon was removed at the end of 24 hours, and the remaining one-fourth removed after 36 hours. There were no bleeding and no fever. She received 300,000 units of procaine penicillin twice daily. She was discharged on May 22, two days after readmission.

Could this patient's intrapartum rise in blood pressure, her prolonged labor, and her postpartum hemorrhage be based on her emotional state? Could this complication have been prevented by a better psychological preparation? We inquire of Dr. Gainey if there have been any emotional factors noted in his patients.

The whole process of involution is a fascinating one. The changes are considered physiologic, but they most certainly border upon the pathologic. As Dr. Eastman has said, "Under no other circumstances does such marked and rapid tissue catabolism occur without a departure from a condition of health." The truly amazing thing is that we do not have a higher incidence of noninvolution or subinvolution. Dr. Gainey reports an incidence of 1:775 in his review of 5,429 deliveries. A review of our records reveals one case in the last 2,000 deliveries.

We heartily concur with Dr. Gainey's conservative and able management, with special re-emphasis upon replacement of blood and control of the bleeding by a tight uterovaginal tampon. We have a dictum that, when packing a uterus and vagina for postpartum bleeding, you should manually place all of the packing possible into the uterovaginal canal and then *add some more.* We have never seen a patient bleed through such a packing. If one should, we would perform total hysterectomy and not repack the uterus.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—If one could take 500 or 1,000 consecutive normal cases and examine the placental site, one might gain a definite understanding of the process. This, however, is impossible. Thus one must approach the subject much as Dr. Gainey has—namely, through the study of a particular complication involving the placental site.

Findings in these patients may be identical with the normal, but this is doubtful. If, however, the histology is identical, then some extraneous cause for the bleeding must be responsible. Such possible causes include bacterial action dissolving out clots and necrotic tissue with resultant hemorrhage, a bleeding dyscrasia from any one of a number of conditions, and hyperheparinemia.

These bleeding patients of course exhibit a psychological disturbance because of the readmission to the hospital and separation from the new child and family.

Two years ago my colleagues and I reported on some of the bacterial findings in uteri removed for various conditions during the puerperium. A bacterial flora persisted until the placental site had healed. One patient went 120 days without bleeding, yet placental tissue was present and so were bacteria. Thus the significance and the nature of the microbiology of the postpartum uterine cavity need further study.

We have intentionally left intrauterine (postpartum) packs in for four to six days. Some are expelled into the vagina. Very few develop any sign of infection. Thus far we doubt that this procedure will change the bacterial flora.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.—In regard to packing the uterus, it seems important, for the sake of clear thinking, to differentiate immediate postpartum packing for immediate postpartum hemorrhage and delayed packing for bleeding which occurs a week or more after delivery. The cause of the bleeding in the latter circumstance is retained placental fragments or subinvolution of the placental site. The cause of the bleeding immeditely post partum is usually uterine relaxation. Whatever remarks I may have made from time to time against packing the uterus had to do with immediate postpartum packing. That seems to me a different issue from the one under consideration now.

The objections to packing the uterus immediately post partum, it seems to me, are several. After curettage, let us say, of a bone diseased with osteomyelitis, you pack a hard surface and you can compress the bleeding point because you are pressing the gauze against a hard surface. The same applies to packing the pelvis in gynecological surgery when there are oozing bleeding points. You are packing against a resistant surface, and thereby you gain compression. When you pack a postpartum uterus, however, that is suffering from relaxation, you are packing a flabby bag; you are packing against nothing. You can get little or no compression by so doing; and compression, as far as I know, is the whole purpose of packing.

Let us suppose, however, that when you first put in your pack immediately post partum, you do get some compression. Then let the uterus relax ever so little, and the uterine wall moves a millimeter or two away from your pack. All compression or contact between your pack and the uterine wall has disappeared.

Furthermore, all efforts in the treatment of postpartum hemorrhage are designed to favor contraction of the uterus, so that the uterine cavity becomes as small as possible.

When you put in a pack you disregard that general objective, and the more gauze you put in, the more you stretch the uterus. These theoretical objections to packing the uterus seem, to me, valid.

From a practical viewpoint, they never pack the uterus in Great Britain, and their results in respect to postpartum hemorrhage are certainly as good as ours. In our own clinic we stopped packing the uterus for immediate postpartum hemorrhage at least 15 years ago, and we have had no cause to regret this policy. We believe that bimanual compression of the uterus is preferable. In desperate cases, especially in multiparas, hysterectomy is occasionally the procedure of choice.

That is the case, as I see it, against packing the uterus for immediate postpartum hemorrhage. Let me remark in conclusion, however, that these comments are not pertinent to Dr. Thomas' case, and I certainly wouldn't take issue with Dr. Thomas in the packing of his case. There he had a uterus 10 days post partum, in which perhaps some resistance was offered by the uterine wall. We have never had to pack any of these late cases, but we do not feel that any remarks which have been made about packing in cases of late puerperal hemorrhage are pertinent to the more common issue—namely, the pros and cons of packing the uterus for immediate postpartum hemorrhage.

DR. A. N. CREADICK, Rocky Hill, Conn.—I wrote Dr. Gainey in August that if he chose to establish a new entity, he must fulfill three requirements: (1) rule out all other possible co-existing causes for the symptom; (2) show some specific pathological changes for this lesion; and (3) establish a definite method of procedure for handling this lesion. You heard his response in the paper he has just read. As regards the first point, it would be necessary to exclude other factors which might be responsible for this condition, such as afibrinogenemia or hypoproacceleranemia. I would not have suggested these bizarre blood changes except that Dr. Robert Creadick had just demonstrated one of them to me. Prior to the demonstration of the 3 cases by Hertig and Rutherford in 1945, extensive blood studies had not been performed on these cases, but I used them as examples of what I meant by excluding other causes of hemorrhage.

Rutherford and Hertig said that they wrote their article "to emphasize the fact that there may be failure of involution of the placental site itself without the associated picture of subinvolution as it has been described or without the retention of placental tissue. This would represent failure of physiologic process of obliteration of the large vessels underlying the placental site." That being the case, the only incident they had that they could produce as evidence was the case in which a hysterectomy had been done. In that case shades of villi vitiated the whole story, because that was obviously a retained polyp.

I think the question is still open, and what I would like to say to Dr. Gainey can be put in a few simple questions: (1) Why should a simple curettage and Ergotrate cure these cases? (2) Is Dr. Gainey looking for a morphological answer for a bleeding diathesis? (3) If this is a disease of the placental site, why does not the same disorder occur in the other vessels from previous placental sites in a grand multipara? (4) Does Dr. Gainey have any slides to show that blood vessel closure following curettage is more efficient than it was in the old granulomatous site? (5) Does he agree that no curettage is efficient enough to rule out placental polyp or other retained secundines?

One contribution Dr. Gainey made was the performance of a digital examination of the uterine cavity. None of the previous articles on this subject have reported such an examination except in unusual instances. The fact that he could get a finger in the canal and palpate the lining of the uterus does much to establish failure of involution of the placental site as a separate entity, distinct from the general subinvolution of the uterine cavity with which we are so familiar.

DR. GAINEY (Closing).—In reply to one of Dr. Creadick's questions, we had only two specimens available. One specimen was given to us by Dr. John F. Wanless of San Diego, California, and we compared it histologically with two other specimens of normal

postpartum uteri removed at autopsy. The dates were comparable. The first normal uterus came from a patient who died five days post partum from polio, and the other from a patient who died three days post partum from a cerebral accident. We could not differentiate the two normal postpartum placental sites histologically from the so-called noninvolution of the placental site. Our conclusion, with what material we have available, is far from conclusive at the present time. No bacteriological studies were done.

As to the question about packing, we feel as does Dr. Eastman that these cases are different and that the occasion for packing the immediate postpartum uterus is rare.

The use of curettage in these cases is analogous to the removal of clots from the prostatic and tonsillar beds in cases of delayed postoperative hemorrhage from these sites.

The clotting time was determined in only one patient, and was found normal. From the manner in which the blood clotted in these patients, however, it was our clinical impression that there was no deficiency of the clotting mechanism or any acquired bleeding diathesis. I can say that, as a result of the massive hemorrhage, these patients may be predisposed to deficiencies contributing to incoagulability of blood in the hours that follow, and this possibility should not be overlooked. In the presence of these bleeding states, hysterectomy, of course, will not solve the problem, as it is not possible to secure hemostasis. This problem requires specific replacement to correct the coagulation defect.

This is a very striking clinical picture, and so far we have been successful in managing it with curettage. Probably thorough débridement of the placental site is more important than the pack.

THE EFFECTS OF EXCESSIVE AMOUNTS OF DIETHYLSTILBESTROL ON EXPERIMENTAL ENDOMETRIOSIS IN MONKEYS*†

ROGER B. SCOTT, M.D., CLEVELAND, OHIO, AND
LAWRENCE R. WHARTON, JR., M.D., BALTIMORE, MD.

(From the Department of Obstetrics and Gynecology, Western Reserve University School of Medicine, Cleveland, and the Department of Gynecology, Johns Hopkins University School of Medicine, Baltimore)

THERE has been no quarrel with Sampson's original tenet that the endometrium of ectopic endometriosis and uterine endometrium are similar in histologic characteristics. In fact, the disease of external endometriosis is unique in this respect: it represents an entity in which a normal mucous membrane infiltrates, invades, and destroys like a cancer.

There has been considerable disagreement as to the hormonal responsiveness of this ectopically located endometrium. It can show a proliferative change or a secretory pattern; it can bleed (apparently shed); or it can show a decidual response to pregnancy. These changes, however, are inconsistent and can be but infrequently correlated in any given patient with the cyclic pattern of the normally located endometrium. This fact has prompted much conjecturing, the major proportion of which ascribed this differential histologic response to its origin by metaplasia from celomic epithelium.[23]

Be this as it may, it is generally agreed from clinical experience that external endometriosis does not progress postmenopausally (barring malignant transformation), and that it is generally quiescent during pregnancy. On the one hand, it seems to abate with the menopausal cessation of active ovarian function, and, on the other, it seems to respond favorably to the extremes of hormonal influence.

It has therefore been advised that normally menstruating women with symptomatic endometriosis be treated with large doses of estrogens. It is argued that this treatment would mimic the effect of the large amounts of estrogens manufactured by the placenta during pregnancy, and in turn would inhibit the ovary, pituitary, and ovarian cycle. Such a treatment pattern would seem unsound without the addition of large amounts of progesterone and chorionic gonadotropins, as well as other factors present during a normal pregnancy.

Since experimental endometriosis has been produced in the rhesus monkey, this animal was chosen for an investigation of the influence of large amounts of estrogen on this disease process. The rhesus monkey is a cyclically menstruating primate; it has a reproductive physiology similar to that of the hu-

*This work was done in part under an American Cancer Society grant recommended by the Committee on Growth of the National Research Council and in part under a Public Health Service Grant (G-3891).

†Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

man female; in contrast to most lower animals, it probably has patent uterotubal junctions without an effective valvelike mechanism; and spontaneous external endometriosis has been found on at least four occasions in this animal. Accordingly, as much as one may dislike to use any lower animal for testing the behavior of human disease entities, this animal seems to be the least objectionable. Hartman states, "The difference between monkey and man, so far as reproductive physiology is concerned, would seem of minor, the points of similarity of major importance, which should give the monkey a high score as an experimental animal for the gynecologist."

Micronized diethylstilbestrol in refined sesame oil (Bio-des R*), 25 mg. per cubic centimeter, was used. Intramuscular injections were given daily for six out of every seven days, beginning with 0.8 mg. per injection. The daily dose was initially doubled each month, and later two of the animals were changed to a constant daily dose. The total amount of stilbestrol injected varied from 390 mg. to 36,560 mg. over a period of time which varied from 3½ months to 24 months.

MONKEY 883.—This animal had a hysterotomy performed on May 6, 1948, during a gestation estimated to be of 130 to 145 days' duration. Surgically excised endometrium at this time was transplanted to the anterior and posterior uterine surfaces, under one round ligament, in one mesosalpinx, in one ovary, on the bladder peritoneum, on the outer surface of the cecum and rectum, in the abdominal incision, and in the anterior chamber of the left eye. Exploratory laparotomies revealed many areas of active endometriosis; these exploratory procedures were performed one year, one and one-half years, and three and one-half years after the original transplantation. This endometrium of pregnancy did not survive in as many areas as was found when (in separate experiments) the nonpregnant endometrium was surgically transplanted. Two months before beginning stilbestrol, abdominal exploration revealed an 8 mm. nodule of endometriosis at the right uterine cornu; a biopsy verified the gross impression. Cyclic menstruation was normal at 24 to 46 day intervals for over one year before stilbestrol was started.

Stilbestrol in oil was started on Dec. 3, 1951, at a level of 0.8 mg. a day, and the daily dose was doubled each month until 400 mg. was given each day. Marked contracture flexion of the legs developed. Four months after beginning the injections biopsies of the sigmoid surface and the abdominal incision revealed endometriosis of histologic type similar to that found in the areas at the right cornu (preinjection study). There was no vaginal bleeding from the beginning of the injections until one day before death—an interval of 10½ months. There was heavy vaginal bleeding on Oct. 18, 1952, and the animal was found dead in its cage the following morning. Apparently death was a result of exsanguination. A total of 15,350 mg. of stilbestrol was given over 10½ months.

At autopsy the uterus, omentum, and intestines were adherent to the under surface of the abdominal scar. The uterine endometrium was thickened and the bladder mucosa was hemorrhagic. The adrenals were enlarged to about three times their normal size. Sections of the uterus revealed complete hyalinization with some necrosis of the endometrium and much of the myometrium; also, there was considerable thickening of the few arterial walls which could be identified. Outside the uterus several areas of endometriosis were identified, particularly near the right cornu, and this tissue was rather inactive in appearance except for some excessive nuclear staining variability. One area of very recent hemorrhage was found in this endometriosis about the uterus, and there was a similar hemorrhage in an endometrial cyst adjacent to one ovary. The ovaries were atrophic, although some developing follicles were seen; there was no old or new lutein tissue. Sec-

*The diethylstilbestrol in sesame oil (Bio-des R) was generously supplied by the Grant Chemical Company, Inc., New York, N. Y.

tions of the Fallopian tube showed atrophic stroma but active, irregular epithelium with marked nuclear variability and nuclear extrusions; a tiny focus of endometriosis was identified beneath the tubal serosa. The vagina showed one-half of the epithelium to be keratinized, and there was a zone of subepithelial collagenous change. Endometrial glandular epithelium was found in one of four lymph nodes identified. Sections of the bowel, pancreas, spleen, liver, kidneys, and lungs were not remarkable.

Summary of Monkey 883.—External endometriosis was produced by the surgical transplantation of the endometrium of pregnancy. Three and one-half years later stilbestrol was started, the daily dose being increased from 0.8 mg. to 400 mg. over 10½ months for a total of 15,350 mg. Cyclic bleeding ceased, but the animal died of heavy vaginal bleeding which began the day before death. Endometriosis was still present outside the uterus, about one ovary, and in one tubal wall, and there were two areas of very recent hemorrhage. The uterine endometrium and much of the myometrium were replaced by hyaline and necrotic tissue. The vagina showed some excess surface keratin and a collagenous change in the subepithelial tissue. The tubal epithelium was quite active. A focus of endometrium was found in one lymph node. The adrenals were enlarged.

MONKEY 889.—This animal has been reported upon previously.[28] She developed endometriosis following an incision across the low cervix and a shifting of the rest of the uterus in order that she would menstruate into the abdomen. This operation was performed on Jan. 21, 1949, and endometriosis was proved histologically 185 days later. On Oct. 16, 1951, an exploratory operation revealed endometriosis with marked deposition of pigment in macrophages outside the uterus and also in the abdominal incision.

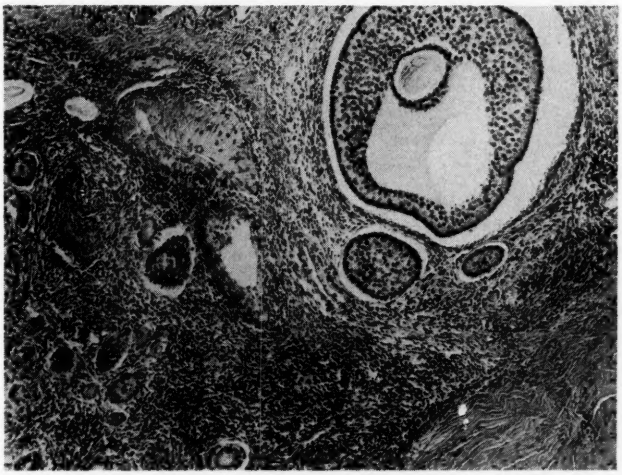

Fig. 1.—Monkey 889. Somewhat atrophic and inactive ovary after three and one-half months of stilbestrol. There are developing follicles, but no new or recent lutein tissue. (×100, reduced ⅕.)

Stilbestrol was started on Nov. 14, 1951, at a daily dose schedule of 0.8 mg., doubled each month until a daily dose of 6 mg. was reached at the time of death. The animal began to bleed vaginally 9 days before death and continued to have heavy bleeding despite doubling of the estrogen dose. A total of 390 mg. of stilbestrol was given over 3½ months. She died on Feb. 23, 1952, apparently from excessive blood loss, but the autopsy was not performed until 2 days later.

At autopsy there were extensive firm adhesions of the reversed uterus to the cecum and sigmoid. The left ovary was quite small and the right ovary could not be identified. The cervix appeared healthy, but there was a large hematoma in the right vaginal wall; this seemed to be the source of the vaginal bleeding. The uterine endometrium was thick and smooth, and the bladder mucosa was hemorrhagic. Microscopically endometriosis was

identified in the posterior cul-de-sac, about the turned uterus, about one ovary, and in the wall of both the large and small intestines. This endometriosis was rather active in appearance, but not hyperplastic, and there were no areas of hemorrhage. The uterine endometrium was of the active interval phase without hyperplasia of the glands or stroma. The endometrial arterioles appeared normal. The cervix showed a spotty metaplasia of the "reserve-cell type," and the squamous epithelium in its lower portion was hyperplastic, as was the vaginal epithelium. In addition the vaginal epithelium was keratinized for one-third to one-half of its outer surface. One area in the apex of the vagina showed only hyaline tissue with necrosis. Near the ovary a large lymph node contained four foci of endometrial glands. The one ovary identified was atrophic (Fig. 1), but there were a few developing follicles and no old or new lutein tissue. The adrenals, unfortunately, were not studied. The lungs were normal.

Summary of Monkey 889.—External endometriosis was produced by surgical shifting of the uterus to allow intra-abdominal menstrual flow. Almost three years later stilbestrol was started, the daily dose being increased from 0.8 mg. to 6 mg. over 3½ months, for a total of 390 mg. Vaginal bleeding of serious proportions continued for 9 days before death. Autopsy revealed a probable source of the bleeding at the vaginal apex, adjacent to and not in the remaining cervix. Endometriosis of an active type, without evidence of recent hemorrhage, was found about the turned uterus, about one ovary, in the obliterated cul-de-sac, and in the intestinal walls. The uterine endometrium was of the active interval type, but it was not hyperplastic. The cervix and vagina showed some increased hyperplasia in the lower epithelial elements, squamous metaplasia of the "reserve-cell type" in the cervical epithelium, and increased keratinization of the vaginal epithelium. One area in the vagina revealed only hyalinized and necrotic tissue with hemorrhage. One lymph node near the identifiable ovary showed four endometrial glands. The ovary revealed developing follicles, but no recent or old lutein tissue.

MONKEY 873.—On Nov. 5, 1948, the right ovary with its attached blood supply was placed within the uterine cavity via an incision in the right uterine cornu. This ovary was passed per vaginam within about one month. On Nov. 29, 1948, endometrial tissue was surgically excised and transplanted to the left ovary, to the right broad ligament, beneath the bladder peritoneum, on the posterior uterine surface, on the peritoneal surface of the rectum, and in the abdominal incision. On Sept. 19, 1951, gross and microscopic endometriosis was identified on the bowel wall and near the left ovary. The menses were normal, occurring at 21 to 44 day intervals.

Stilbestrol was started on Nov. 17, 1951, at a daily dose of 0.8 mg., doubled each month over the next eleven months, until the daily dose was 400 mg. Marked flexion contracture of the legs developed. An exploratory laparotomy on Oct. 21, 1952, was mechanically quite difficult because of extensive adhesions, but a small area of rather active endometrium was identified by biopsy from the left side of the uterus. Stilbestrol was continued at a daily level of 12.5 mg. from Oct. 22, 1952, until autopsy on Nov. 13, 1953. The animal received a total of 36,560 mg. of stilbestrol over 24 months. There was no vaginal bleeding from Nov. 16, 1951, until an episode of 12 days of bleeding beginning Nov. 18, 1952, four days of bleeding beginning Jan. 24, 1953, and scant spotting Feb. 14, 19, and 28, and March 10 and 14, 1953.

Autopsy on Nov. 13, 1953, revealed both large and small bowel adherent to the uterus. All the transplants (except the one in the abdominal incision) were recognized as firm nodules 4 to 5 mm. in diameter, and the left ovary was 4 mm. in diameter and quite atrophic in appearance. The uterine endometrium was quite thick with a grossly cystic appearance, and microscopically there were cystic hyperplasia of the endometrium and hyaline thickening of the endometrial arterioles. There was extensive squamous metaplasia of the "reserve-cell type" in the endocervix; the lower third of the squamous epithelium showed a mild cellular hyperplasia, and the upper third of the epithelium was keratinized. Half of the vaginal epithelium was keratinized, and there was subepithelial round-cell infiltration and a subepithelial zone of collagenous change. This subepithelial collagenous change was also seen in the cervix. The ovary was completely atrophic, with only a rare and tiny follicle, and the endometrial tissue about this ovary showed marked nuclear activity, as did the

tubal epithelium—in fact some areas of tubal epithelium were so extremely altered that they suggested a malignant transformation (Fig. 2). The nodules of endometriosis all showed marked epithelial and stromal hyperplasia, with cystic changes in many areas. There was no evidence of old or recent hemorrhage. Two pelvic lymph nodes showed foci of endometrial glands (Fig. 3). The adrenals were hypertrophied. The kidneys, liver, lungs, and brain were normal microscopically.

Fig. 2.

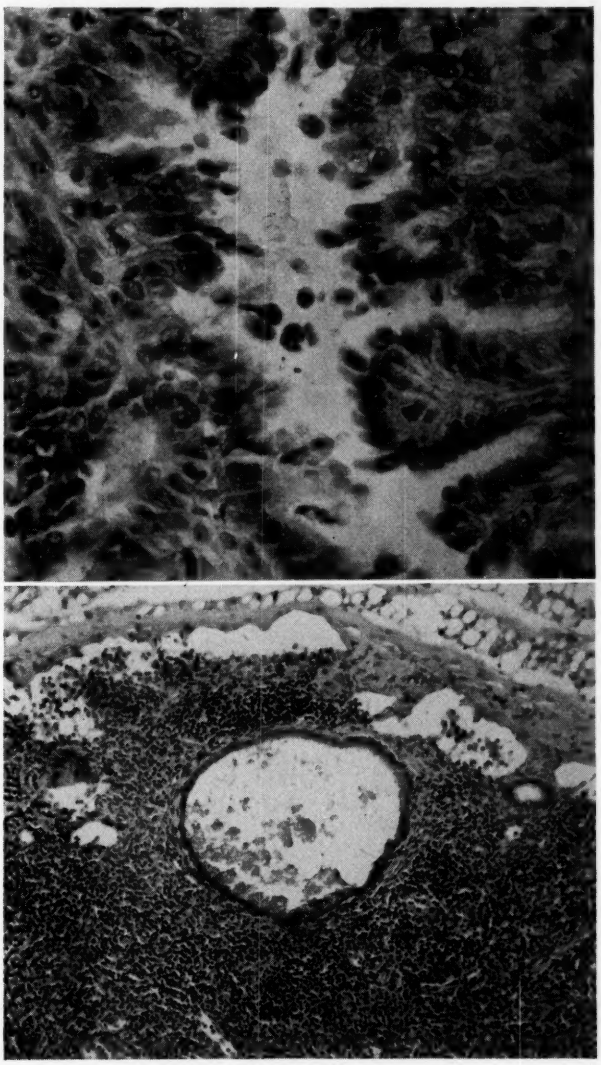

Fig. 3.

Fig. 2.—Monkey 873. Tubal epithelium with marked nuclear activity and variability and extruded nuclei. This change occurred 24 months after stilbestrol injections were initiated. (×500, reduced ⅕.)

Fig. 3.—Monkey 873. Foci of endometrial epithelium in a pelvic lymph node, four years after experimental pelvic endometriosis was produced by transplantation. Six monkeys with endometriosis have now shown such foci in pelvic lymph nodes. (×125, reduced ⅕.)

Summary of Monkey 873.—External endometriosis was produced by the surgical transplantation of endometrium. Approximately two years later stilbestrol was started at a daily level of 0.8 mg. and the daily dose doubled each month for 11 months, when 400 mg. per day was reached. The animal was then maintained on a daily dose of 12.5 mg.

over the subsequent 13 months, and there were several episodes of irregular vaginal bleeding during the first five months of this latter 13 months. A total of 36,560 mg. of stilbestrol was given over 24 months. Autopsy revealed endometriosis present in practically all the transplantation sites, and the endometrial epithelium was hyperplastic. Nuclear changes here and in the tubal epithelium were of near-malignant type. The uterine endometrium was thick, with marked cystic hyperplasia, and the endometrial arterioles revealed slight hyaline thickening. The cervical and vaginal mucosa showed excess surface keratin, increased activity in the lower epithelial zones, subepithelial round-cell infiltration, and collagenous change and squamous metaplasia in the endocervix. The ovary was almost completely atrophied. Endometrial glands were found in two pelvic lymph nodes. The adrenal glands were enlarged.

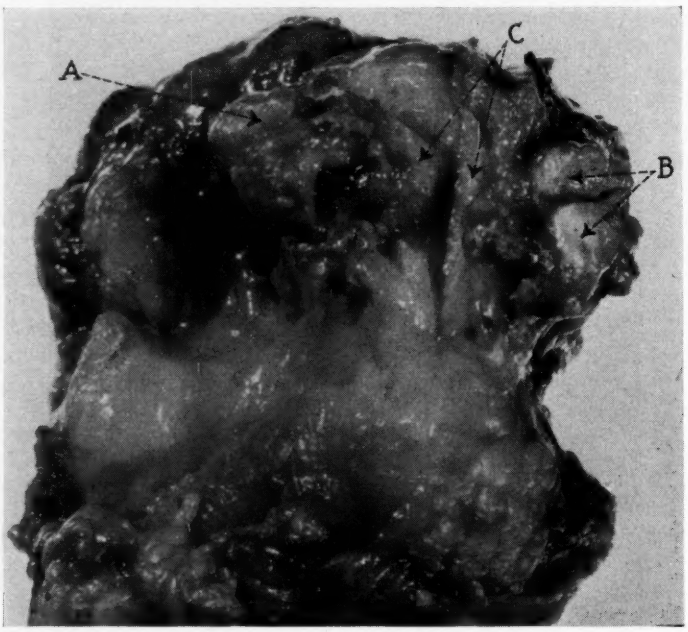

Fig. 4.—Monkey 705. Gross autopsy specimen 23 months after stilbestrol injections were initiated. *A*, Atrophic left ovary. *B*, Opened atrophic right ovary. *C*, Opened uterus. Surrounding these structures are extensive adhesions and external endometriosis.

MONKEY 705.—This animal was transferred to our colony by Dr. George W. Corner. He received it from Dr. Carpenter, who had followed the animal through three term pregnancies and one spontaneous abortion since 1939. An exploratory laparotomy was done to inspect the ovaries in 1940. The animal menstruated at 26 to 35 day intervals. In June, 1951, extensive endometriosis was found in the pelvis; a large endometrial cyst encased the uterus, tubes, and ovaries. This animal has been reported upon as an example of spontaneous endometriosis in the rhesus monkey.[26] Stilbestrol was begun on Dec. 11, 1951, at a daily level of 0.8 mg., and the daily dose was doubled each month over the next six months until 300 mg. was given each day. An exploratory operation at this time revealed active endometriosis in the cyst wall, but the cyst fluid was a clear, serous type. There had been no vaginal bleeding since stilbestrol administration was started. Treatment was allowed to lapse for four months and there was a menstrual flow at the end of this time. Stilbestrol was resumed on Oct. 22, 1952, and continued until November 12, 1953—the day of autopsy. The animal received a total of 4,840 mg. over 23 months, with a 4 months' lapse in treatment during this time. At an exploratory operation following the menstrual flow which occurred at the end of the 4 months of treatment lapse, active endometriosis was identified in the cyst wall, and the cyst contents were black.

At autopsy there were extensive adhesions, large fragments of possible endometriosis about the uterus, very smooth and atrophic ovaries, and a thick uterine endometrium (Fig. 4). The uterine endometrium showed a very definite cystic hyperplasia, and the arterioles here were thickened by a marked hyaline replacement (Fig. 5) and a loss of elastic tissue shown by special stains. This hyaline change was present, though much less marked, in the myometrial arteries and in the arterioles within the areas of external endometriosis.

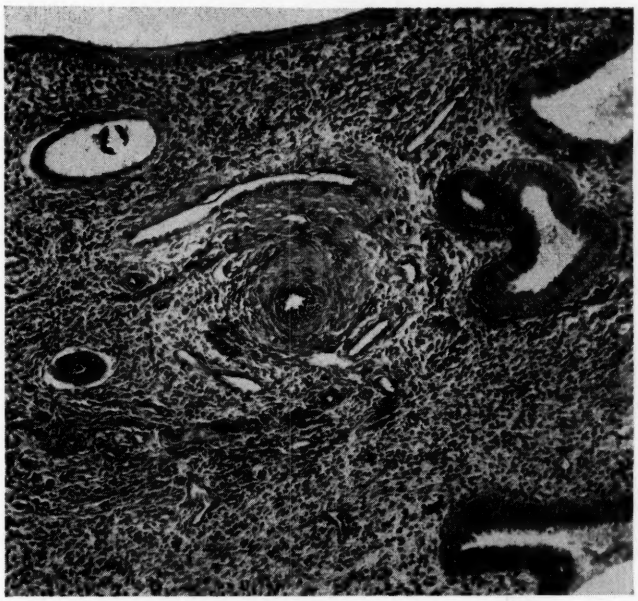

Fig. 5.—Monkey 705. Uterine endometrium from autopsy specimen in Fig. 4. There is cystic glandular hyperplasia, stromal hyperplasia, and a peculiar hyaline thickening and change in the walls of arterioles. (×125, reduced ⅕.)

Fig. 6.—Monkey 705. Cervix of autopsy specimen, showing the thickened epithelium and the squamous metaplasia in the endocervical glands. The subepithelial collagenous change and round-cell infiltration and the surface keratinization are not as marked here as in other animals after stilbestrol. (×30, reduced ⅕.)

There was a small area of adenomyosis within the myometrium. The changes in the cervix and the vagina were the same as described for Monkey 873 (Fig. 6). There was cystic hyperplasia with marked nuclear activity of the endometriosis about the uterus (Figs. 7 and 8) and on the adjacent bowel wall, with two areas of old hemorrhage. The tubal epithelium was very active and wild in appearance. The ovaries were atrophic, with only a rare tiny follicle (Fig. 9). One pelvic lymph node showed endometrial glandular tissue.

Fig. 7.

Fig. 8.

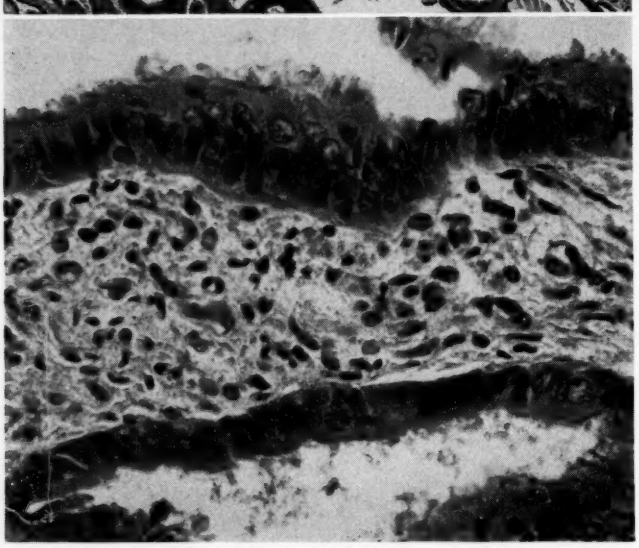

Fig. 7.—Monkey 705. Large focus of external endometriosis about the ovary and tube 23 months after the beginning of stilbestrol injections. There is a marked cystic hyperplasia here, as in the uterine endometrium. (×30, reduced ⅕.)

Fig. 8.—Monkey 705. High power of area of external endometriosis in Fig. 7. Notice the piling up of epithelium, the nuclear variability and the alteration toward a tubal type of epithelium. (×500, reduced ⅕.)

The adrenal glands were enlarged to about three times their normal size. The epithelium of the renal pelvis showed slight surface keratinization, but the kidneys were otherwise normal. The lungs, heart, liver, spleen, and pancreas were normal.

Summary of Monkey 705.—This animal had extensive external endometriosis which was apparently spontaneous in origin. She was given stilbestrol for six months at a daily dose which was increased at monthly intervals from 0.8 mg. to 300 mg. Treatment was allowed to lapse, and was then resumed four months later at a constant daily dose of 12.5 mg. Except for the lapse of four months, treatment was given over a period of 23 months for a total of 4,840 mg. At autopsy extensive external endometriosis of an active cystic-hyperplasia type was present. The uterine endometrium showed cystic hyperplasia and marked hyaline thickening of the arteriolar walls; this hyaline change was less marked in the arteries of the myometrium and the arterioles of the external endometriosis. The epithelium of the cervix and vagina showed an increased surface keratin zone, nuclear activity in the lower zones of the epithelium, subepithelial round-cell infiltration and collagenous change, together with squamous metaplasia in the endocervix. The ovaries were atrophic, with rare tiny follicles, and the tubal epithelium was quite active. One pelvic lymph node showed endometriosis. The adrenals were enlarged, and the epithelium of the renal pelvis had a narrow zone of surface keratin.

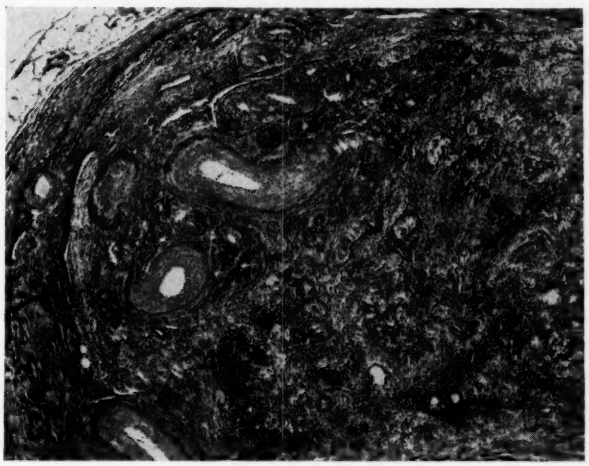

Fig. 9.—Monkey 705. Markedly atrophic ovary as shown in gross of Fig. 4. Only a rare tiny follicle can be identified. (×40, reduced ⅙.)

Comment and Conclusions

The results of prolonged administration of large doses of diethylstilbestrol in sesame oil to 4 rhesus monkeys with external endometriosis were in some respects expected and in other respects unusual and disturbing.

The increased amount of keratin on the epithelial surface of the vaginal and squamous cervical epithelium, as well as the increased nuclear activity of the lower epithelial zones and the subepithelial collagenous change and round-cell infiltration, have been reported following prolonged estrogen administration in monkeys,[2, 5, 7, 10, 25] estrogen plus trauma in monkeys[12, 24] and in rats.[27] Hisaw, Greep, and Fevold[12] noted that the cornification of the vaginal epithelium is decreased and may disappear when progesterone is added. A squamous metaplasia of the endocervical glands was constant, but variable in amount. We found this in previous experiments from trauma and irritation alone—i.e., in the endocervix adjacent to the endometriosis when the monkey's uterus was cut across and turned to permit intra-abdominal men-

struation, and also in endocervical tissue transplanted to other areas. The metaplasia was usually the "reserve-cell type," in which the squamous type of epithelium appeared to arise from beneath the columnar epithelium and continued on to carry a layer of modified columnar epithelium on its luminal surface.

Cystic dilatation of endometrial glands has been noted following protracted treatment with estrone in the mouse, rat, guinea pig, monkey, chimpanzee, and woman. Hisaw[13] observed marked mitotic activity in the glandular endometrial epithelium of monkeys in response to estrone which began to subside after about 30 days, together with the subsidence of the thickness of the endometrium. Engle and Smith[5] reported a thinning of the endometrium of castrated monkeys on estrogen for 100 days or more (apparently an endometrial exhaustion). Hartman, Geschickter, and Speert[10] gave 20 young rhesus monkeys large doses of estrogens for periods up to 18 months and in one animal with the longest treatment endometrial hyperplasia developed. Zuckerman[30] produced endometrial hyperplasia in a castrate monkey after one year of daily estrone, and Engle, Krakower, and Haagensen[7] found this in 2 of 5 aged monkeys after prolonged estrogen. Dahl-Iversen, Hamburger, and Hjørdis[4] were not able to produce endometrial hyperplasia in rhesus monkeys on estrogen administration in a period up to 15 months.

It appears that prolonged estrogen administration to rhesus monkeys produces endometrial exhaustion most commonly but large and/or prolonged doses can result in endometrial hyperplasia. The response of the uterine endometrium in the present experiments was variable, but in the 2 animals receiving estrogens for the longest time (23 and 24 months, respectively) typical thick endometrium of the cystic hyperplasia type was found. One monkey which received estrogen for 3½ months bled to death, and the only apparent source of hemorrhage was a necrotic zone at the apex of the vagina; the uterine endometrium was active in appearance, but not hyperplastic. The fourth monkey received estrogen for 10½ months and died of uterine hemorrhage; the entire endometrium and much of the myometrium showed a diffuse hyaline necrosis.

The hyaline necrosis in the uterus and at the apex of the vagina is difficult to explain. It could be an extension of the subepithelial collagenous change which was seen, or it could be a terminal result of the hyaline thickening of the endometrial arterioles seen in Monkey 705 and Monkey 873. This change was less marked in the myometrial arteries, and some could be seen in the areas of external endometriosis. Engle, Krakower, and Haagensen[7] noted this vascular change in 3 of their animals. It could be termed an extreme and rapid aging of the uterine vessels resulting from prolonged excessive doses of estrogen without the possible counteracting benefits of progesterone.

Cyclic menstrual bleeding ceased in these animals. Bleeding with fatal results in the two animals previously noted began shortly before death. Monkey 873 had irregular spotting for five months when the estrogen dose was changed from an increasing to a constant daily dose, and Monkey 705 had

one episode of vaginal bleeding when the estrogen administration was allowed to lapse. The ovarian atrophy, the absence of lutein cells (old or new) in the ovaries, and the type of uterine endometrium suggest that ovarian function and, more particularly, ovulation were inhibited.

The external endometriosis had been produced experimentally in 3 monkeys, and it was of spontaneous occurrence in the fourth animal. In 2 animals the endometrium was surgically excised and transplanted onto and into various pelvic organs, as well as in the abdominal incision. Viable transplants were grossly and microscopically identified over two to three and one-half years later, prior to the administration of the stilbestrol. The experimental endometriosis in one animal was produced three years before by the method of shifting the uterus to allow intra-abdominal menstruation, and the presence of this disease here, as in the animal with spontaneous endometriosis, was histologically proved before the experiments were undertaken.

Micronized diethylstilbestrol in sesame oil was given over 3½ to 24 months, in total doses of 390 to 36,560 mg. In all instances the external endometriosis was still present in essentially all the original areas. There was no evidence of atrophy or freeing of adhesions; in fact, the areas were usually grossly larger, and in the 2 animals with cystic hyperplasia of the uterine endometrium there was cystic hyperplasia in many of the areas of external endometriosis. The glandular epithelium in all instances showed minimal to marked nuclear activity; longer administration increased these changes with piling up of the epithelium to a point of appearing quite "wild." Much of the epithelium tended toward a tubal type. Activity of the stroma in the ectopic endometrium was not marked until after longer administration and concomitant with the development of cystic hyperplasia.

Some of the ectopic endometrium responded, in so far as hemorrhage was concerned, in much the same manner as the normally located endometrium. For example:

1. Monkey 883.—This animal died of a uterine hemorrhage. Autopsy revealed two areas of recent hemorrhage in the ectopic endometrium, one of which was a small endometrial cyst filled with blood.

2. Monkey 889.—This animal died of an unexplainable hemorrhage from the vaginal fornix. Otherwise it did not show evidence of uterine bleeding during the treatment, and there was no old or recent evidence of hemorrhage in the endometriosis.

3. Monkey 873.—Uterine spotting occurred 8 months before death, when the estrogen was changed to a constant daily dose. There was no old pigment or recent hemorrhage in the endometriosis.

4. Monkey 705.—Pretreatment studies revealed the endometrial cyst to contain tarry material. After six months of estrogen and no vaginal bleeding the cyst contents became thin and serous; but they again became tarry after treatment lapse and an episode of menstrual flow.

It is known that progesterone withdrawal from an estrogen-primed endometrium will cause sloughing of the endometrial surface. It can be postu-

lated that, in the absence of extensive fibrotic encasement (and therefore assuming an adequate blood supply), areas of ectopic endometrium will respond to these same circulating hormones. Fragmentation, infiltration, spread, and subsequent growth could then occur ectopically. This is a theory to explain the growth pattern of ectopic endometrium. To extend this, it can be postulated that ectopic endometrium may be as capable of menstrual sloughing (when the blood supply is adequate) as is the uterine endometrium when there is withdrawal of, or variations in, the estrogen levels. The correlation between uterine bleeding and the findings in the external endometriosis lends some support to this hypothesis.

There are other findings which might be briefly mentioned. The tubal epithelium, but not the stroma, in these treated animals generally became quite active, with nuclear alterations, some piling up, and nuclear extrusion via "cell explosions." The adrenals became definitely hypertrophied and this has been noted after prolonged estrogen administration in animals.

The pelvic lymph nodes were studied in all of these animals, a precaution not taken in most of our other autopsies. All 4 animals showed endometriosis in one or more of the pelvic lymph nodes. Monkey 874 (previously reported[26]) and Monkey 895, both with experimentally produced endometriosis, have also shown pelvic lymph nodes which were positive for endometriosis. Thus 6 monkeys with external endometriosis all had endometrial tissue in pelvic lymph nodes—the finding was 100 per cent in the animals specifically studied for this. Lymphatic spread of endometrium may be much more likely than was formerly suspected, as Javert[18] has indicated.

Pfeiffer and Allen[25] reported the contracture of the thighs from atrophy of the hamstrings after estrogen administration and 2 of our animals developed this to a marked degree.

Hazards are constantly present when an attempt is made to transfer results of animal experiments to clinical experiences with human beings. The rhesus monkey, as a cyclically menstruating animal, appears to be nearly ideal for experimental study of female hormonal responses. However, Corner[3] has questioned whether the metabolism of progesterone is the same in the two species; Van Wagenen and Gardner[29] have shown that intrasplenic ovarian transplants become systemically functional and that the liver does not destroy estrogens as it does in lower animals (the human female may be more akin to the monkey in this respect); and Kaiser reported cyclic menstruation in a South American monkey *without* evidence of spiral arterioles in the endometrium. Furthermore, the doses of synthetic estrogen were extreme and entirely unphysiologic, and the required amount of sesame oil to carry this hormone may have accounted for some of the peculiar results.

In the clinical treatment of external endometriosis, Karnaky[21] has recommended increasingly large doses of stilbestrol over several months and Bickers,[1] Hurxthal and Smith,[17] and Hulme and Holmstrom[16] all suggested a smaller dose for a part of the menstrual cycle to inhibit ovulation. None of these studies are well controlled; the diagnoses were generally made on the basis of clinical findings, and thorough before-and-after histologic studies were

rare and open to question. Gray and Barnes,[9] in one exceptional instance, ran a very complete study on a patient with external endometriosis, using large doses of stilbestrol. Severe episodes of vaginal bleeding were difficult to control; the symptoms and the nodules did not disappear; and the epithelium in the ectopic endometrium became hyperplastic rather than atrophic.

Animal and human studies would indicate that large or moderate amounts of stilbestrol may control the pain and spread of endometriosis by inhibition of the ovaries and of ovulation. The atrophy of the ovaries was certainly evident in the present animal experiments. If the complication of uterine bleeding occurs, however, it can be an even more annoying problem, and, furthermore, if the ectopic endometrium also sheds, nothing has been gained. The increased epithelial activity in the uterine and ectopic endometrium and in the cervical and tubal epithelium, the keratinization and subepithelial collagenous change in the cervix and the vagina, and the hyalinization of the uterine arterioles (? an aging of the genital vessels) could be most disturbing if they occurred in the premenopausal woman to the same extent that they did in these monkeys.

Inhibition of ovarian function may be anything but beneficial for long periods in certain patients. A comparison of the ovaries suppressed by stilbestrol to the ovaries of a pregnant woman is unwarranted; the former are not under the additional protective screen of progesterone or the unknown influences of chorionic gonadotropins and other factors.

Summary

1. Estrogens in large and increasing amounts, as well as in smaller and interrupted amounts, have been recommended for the treatment of external endometriosis.

2. The effect of large doses of diethylstilbestrol (in sesame oil) was experimentally tested on four rhesus monkeys. These animals were cyclically menstruating animals in which there was proved external endometriosis. In three animals the endometriosis had been produced two to three and one-half years prior to the injections, and in the fourth animal it was of spontaneous occurrence.

3. The total dose varied from 390 mg. to 36,560 mg. over three and one-half months to 24 months. At first the daily dose was doubled each month and later the daily dose was a constant figure of 12.5 mg.

4. Two animals died during the course of treatment, both apparently from severe vaginal bleeding. In one animal the bleeding was uterine in origin, and the uterus revealed an extensive hyaline necrosis of the endometrium and much of the myometrium; the other monkey had an exsanguinating hemorrhage apparently from an area of hyaline necrosis in one vaginal fornix.

5. Two animals were treated for 23 and 24 months (except for a lapse of 4 months in one), respectively, and then autopsied. Both showed cystic hyperplasia of the endometrium and a hyaline thickening of the endometrial arterioles, and to a lesser extent of the arteries in the myometrium and the arterioles within the external endometriosis.

6. External endometriosis was identified periodically prior to, through, and at the end of the treatment. There was increased nuclear activity of the epithelium in all instances which was roughly in direct proportion to the duration of treatment; in the two animals treated for the longest periods, cystic endometrial hyperplasia was present in both the ectopic and the uterine endometrium.

7. Cyclic menstruation ceased, although uterine bleeding occurred at some time during the treatment in all of the animals. Evidences of old or recent hemorrhage were found in the ectopic endometrium which could be correlated in each particular animal with the old or recent history of uterine bleeding.

8. From the foregoing it is assumed that bleeding can occur in ectopic endometrium, as well as from uterine endometrium, on continuous or interrupted estrogen administration. Given an absence of extensive fibroblastic encasement and an adequate availability via the blood stream of all hormonal influences, "menstrual sloughing" of ectopic endometrium can occur from the continuous administration or the sudden withdrawal of estrogen, as well as by progesterone withdrawal from an estrogen-primed endometrium. If it is agreed that the menstrually shed fragments of endometrium are viable and can infiltrate via fascial planes, spread by lymphatics, and grow, it is fair to assume that external endometriosis may grow by any mechanism which allows menstrual flow. This hypothesis is conjecture based upon some known facts but subject to much more complete study before it can be critically evaluated.

9. Atrophy of the ovary or ovaries to a variable degree was a constant finding. A rare tiny follicle or several developing follicles without evidence of old or recent lutein cells were found. Probably any advantage in the use of estrogen in endometriosis results from the ovarian atrophy and the inhibition of pituitary function or ovulation. Without the counteracting influence of progesterone and other pregnancy alterations, the over-all effects from estrogen alone cannot be compared to those found during and following a normal pregnancy.

10. Endometrial glands were found in the pelvic lymph nodes of all four of these animals, making a total of six instances of endometriosis in pelvic lymph nodes of rhesus monkeys with experimental or spontaneous endometriosis. This makes an incidence of 100 per cent in all animals with experimental endometriosis in which this alteration was specifically searched for.

11. Further findings to a variable degree in these animals were:

A. Keratinization of the outer portion of the cervical and vaginal squamous epithelium and increased nuclear activity of the lower zones of this epithelium.

B. Subepithelial collagenous change with round-cell infiltration beneath the cervical and vaginal squamous epithelium.

C. Squamous metaplasia of the "reserve-cell type" in the endocervical glands.

D. Increased nuclear activity of the tubal epithelium.

E. Contracture of the thighs secondary to atrophy of the hamstring muscles.

F. Hypertrophy of the adrenal glands.

12. The hazards of adapting limited animal experimentation to clinical medicine, even from the seemingly ideal, cyclically menstruating rhesus monkey, are appreciated. The effects of large amounts of sesame oil are not known. Nevertheless, it would seem that the treatment of external endometriosis with estrogens, particularly with large doses, has no permanent therapeutic value and may be fraught with tissue changes of potential, if not actual, serious import.

This work would not have been possible without the active assistance and encouragement of Dr. George W. Corner and his staff of the Department of Embryology of the Carnegie Institution of Washington, Baltimore, Maryland.

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Discussion

DR. R. R. GREENE, Chicago, Ill.—I shall discuss a few of the clinical implications Dr. Scott has made from his experimental material.

I certainly do not believe that stilbestrol is the universal panacea, nor that it actually cures endometriosis. On the other hand, I do believe that it can be of value in controlling symptoms in selected patients, and that in some instances it causes a decrease in the size

of the lesions. There are occasional disadvantages to its use, but I doubt very much that it causes any permanent harmful tissue changes in the human subject comparable to those reported by Dr. Scott. Even the intense pigmentation that occurs in certain areas on some women seems to fade with time.

We have tissues in the departmental laboratory at Northwestern Medical School from a small group of women who had been given stilbestrol in large daily doses (but not comparable on a weight basis to the tremendous amounts given by Dr. Scott to his monkeys). As in Dr. Scott's monkeys, there seemed to be a variability in the response of different individuals.

We had endometrial biopsies done on 5 patients who had received 100 mg. of stilbestrol daily for three to four months. Three of these 5 patients showed an active hyperplasia of the endometrium. In one, there was an "inactive" hyperplasia; by that, I mean that no mitotic figures were present in the glandular or stromal cells. In the fifth patient, a biopsy done at two and one-half months showed an active hyperplasia; the biopsy was repeated at four months, and the endometrium appeared inactive. From the same group of patients, cervical biopsies were available from 8. Abnormalities in the cervical tissues were not impressive. There was, however, a hyperkeratosis in 4 of the 6 biopsies in which stratified squamous epithelium was available. In addition, there was a glandular hyperplasia in 3 and metaplasia of the endocervical epithelium in 4. I cannot comment on whether this metaplasia was of the "reserve-cell" type or not, since I do not hold with this mystical concept. Tissues were also available from a 33-year-old patient who had received 10 mg. of stilbestrol daily for one year. Grossly, she had a very marked hyperplasia of the endometrium, but microscopically it was inactive.

Finally, there is a very interesting 22-year-old patient of Dr. Byford Heskett's who had extensive endometriosis of the cul-de-sac, the posterior fornix of the vagina, and the cervix. She was given 100 mg. of stilbestrol daily for three months and then again for 18 months—a total of 21 months of treatment. In the original biopsy the endometriosis in the posterior fornix was remarkably active in appearance. After she had received 100 mg. of stilbestrol a day for three months, this endometriosis was much less active in microscopic appearance. After she had been on stilbestrol for 18 months continuously, biopsies from the posterior fornix showed no endometriosis, and the endometrium showed an inactive type of hyperplasia. An extremely thick-walled spiral artery, reminiscent of those depicted by the essayist, was present. One would expect, however, that if a spiral artery persisted for 18 months instead of sloughing after one menstrual cycle, it should have a very thick wall. Incidentally, the absence of endometriosis in the area of biopsy was due to coincidence. We do not mean to imply that the stilbestrol had cured it.

Endometrial biopsy was done six days after discontinuation of the stilbestrol. The endometrial pattern was the same, but the gland cells had gained cytoplasm and mitotic figures were numerous. Another endometrial biopsy was done eighteen days after the stilbestrol was stopped. This showed mixed proliferative and early secretory endometrium with subnuclear vacuoles. It seems very probable that this patient had ovulated. Incidentally, I have data on another patient who took 50 mg. of stilbestrol daily for six months and was kind enough to take morning temperatures after discontinuation of stilbestrol. Judging by her basal temperature graph and by the fact that she became pregnant, this patient ovulated exactly 14 days after discontinuation of the stilbestrol. Some of my confreres have had similar experiences.

I was interested in the fact that Drs. Scott and Wharton found endometriosis in the pelvic lymph glands of all of 6 monkeys with experimental or spontaneous endometriosis. I wonder if they have any data as to the incidence of this condition in the pelvic lymph glands of monkeys without endometriosis.

DR. RALPH E. CAMPBELL, Madison, Wis.—Dr. Hisaw, Dr. Meyer, and I have had many years of close association, and I have benefited from our experience in this field. As a "monkey man," however, I am not in a class with such names as Hisaw, Hartman, Meyer, Corner, and the authors.

Endometriosis does occur in rhesus monkeys, as the authors state. An interesting reference they did not give is "Endometriosis in a Rhesus Monkey," by Kluever and Bartelemez (Surg., Gynec. & Obst. 92: 650, 1951). Endometrium will grow when transplanted to the eyes, as Markee has shown in several papers. Hisaw has demonstrated the growth of transplants in the body cavity of monkeys (in a paper yet unpublished).

Why did the authors give such enormous doses of estrogens? This to a large extent would probably defeat their purpose, if it was to obtain growth and further spreading of the endometrium. It has been established for some time by such investigators as Hisaw, Engle, and Smith, and others that endometrium will not grow indefinitely under constant stimulation of estrogen, even when reasonable doses are given. Hartman has shown that large doses of estrogen given for a long time will reduce the total size of the reproductive tract of an adult monkey to less than one-third that of normal. Hisaw has confirmed Hartman's findings. It is important to note that such treatment does not damage the parts beyond recovery.

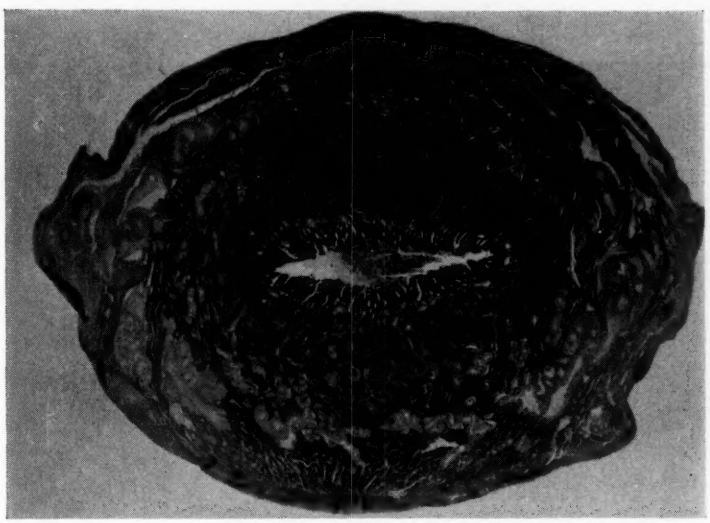

Fig. 1.

The fact that large doses of estrogen inhibit the pituitary and ovarian function and suppress ovulation has been known for some time. The changes in the ovary reported by Dr. Scott are the usual findings.

It is an established fact that high estrogen dosage will retard the growth of endometriosis, but the authors correctly conclude that it will not destroy and thus cure endometriosis. The "monkey men" have known this for quite some time.

Cystic hyperplasia has been mentioned by the authors. This occurs rarely in the monkey. An endometrium may have cystic glands and not be growing, or, at the most, be growing only enough to maintain itself. How can we call such an endometrium hyperplastic?

The hyaline thickening of the endometrium can be produced more easily by giving progesterone alone than by large doses of estrogen. Hisaw's collection of photomicrographs contains a cross section of a uterus showing the condition produced by giving 2 mg. of progesterone daily for 113 days (Fig. 1). Menstruation occurred three days after the last dose. Such uteri are like dishrags, and are very pliable. They bleed profusely when one attempts to do a biopsy. Surprisingly, if a daily dose of 1,000 mg. of estrogen is added to the treatment, the uterine vessels can undergo rejuvenation.

The authors refer to the spiral arterioles and menstruation in a way that seems to imply that monkeys differ from human beings in that these arteries are essential in women but not in monkeys.

Hisaw concurs with Doris Phelps' opinion that the real function of the spiral arteries in both monkeys and women is related to nidation rather than menstruation (Phelps, Doris: Endometrial Vascular Reactions, and the Mechanism of Nidation, J. Anat. 79: 167, 1946). Hisaw states: "It seems that menstruation is a stromal phenomenon which occurs on withdrawal of a supporting stimulus (estrogen or progesterone) and will take place regardless of the thickness of the endometrium or the presence or absence of uterine glands, surface epithelium and coiled arteries" (Anat. Rec. 112: 42, 1952).

Another photomicrograph taken from Hisaw's collection (Fig. 2) shows the uterus of a monkey given 1,000 mg. of estrogen plus 2 mg. of progesterone daily for 200 days. The endometrium is composed entirely of modified stroma, with no glands except small rudiments along the myometrium, and, I emphasize, no spiral arterioles. In this particular monkey, bleeding will take place if treatment is discontinued or if only progesterone is withheld; however, when estrogen is withheld and progesterone is continued, the endometrium crumbles away and there is no bleeding. To be sure, this shows the complexity of the physiologic changes in the endometrium.

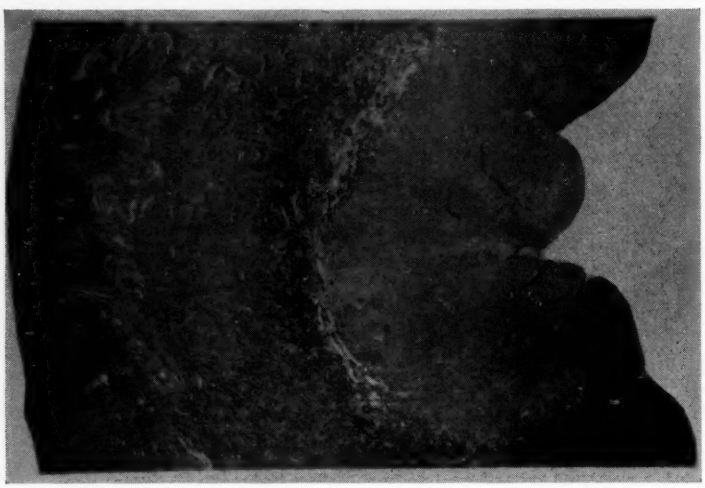

Fig. 2.

Interestingly enough, the authors repeatedly mention squamous-cell and reserve-cell metaplasia of the cervix. Hisaw and others have shown that this same metaplasia, which could not be differentiated from a malignancy, can be completely changed by the administration of progesterone.

I am wondering whether the enlargement of the adrenal glands repeatedly found in relation to high dosage of estrogens is of physiologic importance. The extension of endometriosis to the lymph nodes is significant.

In rats, according to Dr. R. K. Meyer, diethyl stilbestrol has a growth-suppressing effect and the animals, when given large doses, have to be forcibly fed to maintain their nutrition and vitamin balance. In addition, these same animals on continuous diethylstilbestrol treatment initially have an increase and later a decrease in the thyrotropic hormone.

The adrenals in Dr. Scott's monkeys were mentioned consistently as being enlarged; no microscopic reports were given at autopsy, however. Experimentally it has been shown that the adrenalectomized monkey is considerably more sensitive to the estrogens. Are these same factors at work in these monkeys, accounting for the deleterious effects, contractures, and deaths occurring in these experiments?

It would be interesting to compare, in both the castrate and the noncastrate monkey, the effects on ectopic endometrium of estrogen alone, a combination of estrogen and androgen, androgen alone, and finally, and of utmost importance, progesterone alone.

The authors have shown, in this particular investigation in monkeys, that treatment by estrogen has not been effective in reducing the lesions of endometriosis, but has produced additional serious lesions which might be thought of in treating human patients.

Finally, it is my opinion that, if the authors are interested in the growth reactions of endometrial tissue in experimental endometriosis in monkeys, they should not use such large doses of estrogen, and that both estrogen and progesterone should be used in the investigation to make it a little more physiologic. The viewpoint of the authors as clinicians is understood, and that is important.

I commend them for such a time-consuming investigation and for their detailed report, which I have enjoyed tremendously. I hope they will continue their investigation.

DR SCOTT (Closing).—Clinically, we know that the response to estrogens is quite variable. For example, a 73-year-old woman given 1.25 mg. of Premarin daily for three weeks showed a marked endometrial hyperplasia and changes in and about the cervical and vaginal epithelium which were similar to the changes seen in the rhesus monkeys. It appears that estrogens in a premenopausal woman, by inhibiting ovulation, could provide symptomatic relief of endometriosis in particular instances, but would not cure the disease.

I have not studied the lymph nodes in animals without external endometriosis. The expense of the animals has prohibited this until the present time, but plans are at hand for this study.

In answer to Dr. Campbell, the speaker bows in appreciation to the many contributions of Dr. Hisaw to the understanding of the hormonal physiology of the rhesus monkeys. This present experimental study was admittedly and purposely set up to test the results of *unphysiologic* levels of estrogenic hormones. Dr. Campbell has suggested the testing of *physiologic* amounts of estrogens, progesterone, etc., upon the endometrium of rhesus monkeys. Many of these studies have been made previously, and the present study contributes little except to show the effects of excessive amounts of estrogen upon ectopic endometrium. There has been abundant research and abundant literature on the effects of hormones upon *uterine* endometrium. The side results of the present studies are not particularly informative; for example, adrenal hypertrophy following the administration of estrogens has been mentioned frequently. Unfortunately, pathologic study of these enlarged adrenals contributes nothing to the basic understanding. The present experiment should not be misunderstood; the doses of synthetic estrogen were unphysiologic. Dr. Campbell has suggested testing physiologic doses of the various hormones. Not only is this study in progress, but it is being carried out in much the same over-all pattern as Dr. Campbell has mentioned.

The microscopic diagnosis of endometrial hyperplasia in these animals has been questioned. All that can be said is that grossly and microscopically it fits all the criteria for such a diagnosis: the glands are cystic; the epithelium and stroma are active and nonsecretory. I know of no other possible interpretation to place upon these findings.

Attention in these experiments should be focused upon the ectopic endometrium, for the observations concerning the other effects of large doses of estrogens are neither new nor original.

METHODS OF TERMINATING PREGNANCY IN THE PRESENCE OF TOXEMIA WITH SALVAGE OF INFANTS WEIGHING OVER 750 GRAMS*

C. H. Mauzy, M.D., Winston-Salem, N. C.

(From the Department of Obstetrics and Gynecology, The Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital)

A NUMBER of authors[1-4] have emphasized that, in certain types of toxemia, termination of pregnancy may be to the interest of both mother and infant. There is considerable evidence that the persistence of toxemia frequently increases both the maternal and the fetal hazards.[5-7] The prognosis for the infant is particularly unfavorable if eclampsia or abruptio placentae develops. Chronic hypertensive vascular disease is usually associated with a high fetal death rate, which is generally increased threefold if acute toxemia is superimposed.[8, 9] Taylor, Tilman, and Blanchard[10] have laid down certain criteria, including the degree of hypertension and the amount of proteinuria, upon which they base a decision to interrupt pregnancy in a toxemic patient.

It is not the purpose of this paper to discuss the somewhat controversial indications for the termination of pregnancy in toxemia, although we do not believe that it is always advisable to carry the pregnancy to term. We are also not certain that too much emphasis should be placed on the distinction between mild and severe pre-eclampsia. Too often the terms "slight hypertension" and "minimal proteinuria" tend to lull the clinician into a false sense of security. Abruptio placentae and eclampsia may occur even in cases of so-called "mild" pre-eclampsia.

In North Carolina, toxemia is still the leading cause of maternal deaths. Although no figures on the fetal loss in toxemia are available in this state, it is unquestionably high enough to present a real challenge to the clinician.

Management of Cases Complicated by Toxemia of Pregnancy in the North Carolina Baptist Hospital, 1947-1953

We have made a survey of the pregnancies complicated by toxemia which have been seen at the North Carolina Baptist Hospital from 1947 through 1953, and have compared the total salvage rates obtained in cases allowed to wait for the spontaneous onset of labor with those obtained when the pregnancy was terminated by induction of labor with Pitocin or by cesarean section.

Table I shows the incidence of toxemia and the fetal death rate in 8,931 patients delivered at the North Carolina Baptist Hospital from 1947 through 1953 of viable infants weighing 750 grams or more. These were all white women, 80 per cent of whom were private patients. The incidence of toxemia in the private patients was 5.6 per cent, while in the service patients it was 18.3 per cent.

*Presented by invitation at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

Less than 10 per cent of the private patients with toxemia were referred—that is, had not been followed prenatally by the obstetrician responsible for delivery.

TABLE I. INCIDENCE OF TOXEMIA AND FETAL DEATH RATE IN THE NORTH CAROLINA BAPTIST HOSPITAL, 1947-1953

	TOTAL GROUP	TOXEMIC PATIENTS
Number patients delivered	8,931	733 (8.2%)
Perinatal death rate	3.4%	5.7%

Ten patients with hypertensive cardiovascular disease who were delivered of infants that weighed less than 750 grams are omitted from this study. Eight of these pregnancies were terminated by hysterotomy, and 2 patients had spontaneous deliveries. No infant that weighed less than 750 grams and was delivered of a toxemic mother has ever survived in our institution.

Classification of Toxemia.—

I personally reviewed the charts of the 733 patients with toxemia and classified them (Table II) according to the nomenclature and regulations of the American Committee on Maternal Welfare, established on April 1, 1952. However, all of our patients with pre-eclampsia had a diastolic blood pressure of 90 mm. Hg or above, and in no case was the diagnosis made on the basis of edema or albuminuria alone. The small number of cases classified as hypertensive cardiovascular disease is probably misleading. We were often unable to make the diagnosis of hypertensive cardiovascular disease clinically, because the patient was seen for the first time in the second or third trimester of pregnancy. Frequently no antecedent history or record of hypertension existing prior to the pregnancy was obtainable, and in a number of the cases postpartum follow-up was inadequate.

TABLE II. CLASSIFICATION OF TOXEMIA

	PRIVATE	SERVICE	TOTAL
Mild pre-eclampsia	282	207	489
Severe pre-eclampsia	63	52	115
Eclampsia	12	10	22
Hypertensive cardiovascular disease	31	47	78
Hypertensive cardiovascular disease with superimposed toxemia	10	16	26
Unclassified	1	2	3
Total	399	334	733

Method of Termination.—

Table III shows the methods of delivery employed in these 733 cases. The group classified as "spontaneous labor" includes also those cases in which artificial rupture of the membranes was used as a means of induction. Amniotomy was performed only when the cervix was favorable and the presenting part engaged, and these cases represent a very small percentage of the total. This group also includes 2 cases in which a Voorhees' bag was used for induction—a procedure which we condemn.

TABLE III. METHOD OF TERMINATION

	CASES	PERCENTAGE
Spontaneous labor	606	82.6
Induction with Pitocin	104	14.2
Cesarean section	23	3.2
Total	733	100.0

In most instances where Pitocin was used to induce labor, the cervix was long and closed and the presenting part was not engaged. In 6 cases, however, Pitocin was used to stimulate labor which had already begun. In 2 patients Pitocin failed to induce labor, and cesarean section was required.

Only 10 of the 23 cesarean sections were done solely because of toxemia. Other indications were abruptio placentae (4 cases), previous section (5 cases), disproportion (3 cases), and transverse presentation (1 case). The incidence of cesarean section among all deliveries performed during this period of study was 2.3 per cent.

Results in Terms of Fetal Salvage

Correlated With the Method of Termination.—

In Table IV the uncorrected incidence of fetal loss is correlated with the method of termination. Of the 43 fetal deaths, 15 were antepartum, 14 intrapartum, and 14 neonatal. Four babies were dead prior to the use of Pitocin, and 2 in the series with Pitocin-induced labor had anomalies incompatible with life. Two patients had dead babies prior to cesarean section. Among the 11 sets of twins there were 5 deaths—3 in spontaneous deliveries and 2 in a delivery by cesarean section.

TABLE IV. FETAL LOSS CORRELATED WITH METHOD OF DELIVERY

	NUMBER OF INFANTS DELIVERED	FETAL DEATHS	INCIDENCE OF FETAL LOSS (%)
Spontaneous labor	615*	25	4.0
Pitocin-induced labor	105†	11	10.4
Cesarean section	24†	7	28.3
Total	744	43	

*Nine sets of twins.
†One set of twins.

There were 2 cases in which Pitocin induction failed, and termination by cesarean section was required. One was an unclassified case of toxemia without hypertension but with poor renal function. Pitocin was given for six consecutive days without effect on the cervix. The other patient was a 30-year-old multigravida admitted at 37 weeks with severe pre-eclampsia and a breech presentation. She responded poorly to conservative treatment, and received intravenous Pitocin for only one day without change in the cervix. Cesarean section was performed on the sixth hospital day because of progression of the hypertension. In both of these cases the infants survived.

Correlated With the Classification of Toxemia and the Method of Termination.—

In Table V the incidence of fetal loss is correlated with the classification of toxemia and the method of termination. Although the groups are small, the series in which labor was induced by Pitocin compares favorably with those in which labor was spontaneous. It should be pointed out that the cases selected for induction by Pitocin were comparable to those managed by other techniques in regard to the degree of hypertension and albuminuria, except that those in the group with mild pre-eclampsia were clinically advanced cases. In each instance it seemed imperative to us that the uterus be emptied in the interest of either the mother or the child.

The mothers with severe pre-eclampsia had a fetal loss two and one-half times as great as those with mild pre-eclampsia. The fetal loss in cases of hypertensive cardiovascular disease was 5 per cent, and was increased threefold when toxemia was superimposed. One-third of the infants born of eclamptic mothers failed to survive.

TABLE V. FETAL LOSS CORRELATED WITH CLASSIFICATION OF TOXEMIA AND METHOD OF DELIVERY

	LABOR SPONTANEOUS		LABOR INDUCED BY PITOCIN		CESAREAN SECTION		TOTAL		INCIDENCE OF FETAL LOSS (%)
	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	
Mild pre-eclampsia	438	11	48	1	13	5	499	17	3.4
Severe pre-eclampsia	79	4	32	6	5	0	116	10	8.6
Eclampsia	17	6	4	1	1	1	22	8	36.3
Hypertensive cardiovascular disease	61	2	16	2	1	0	78	4	5.1
Hypertensive cardiovascular disease with superimposed toxemia	18	2	5	1	3	1	26	4	15.3
Unclassified	2	0	0	0	1	0	3	0	0
Total	615	25	105	11	24	7	744	43	5.7

Correlated With Weight and Method of Termination (Table VI).—

Twenty-six of the 43 fetal deaths were in premature infants (weight less than 2,500 grams). The incidence of prematurity in the entire group of toxemic patients was 11.5 per cent, with a fetal loss of 30 per cent. The incidence of prematurity in all deliveries during this period was 9.2 per cent.

TABLE VI. LOSS CORRELATED WITH FETAL WEIGHT AND METHOD OF DELIVERY

WEIGHT AT BIRTH (GRAMS)	LABOR SPONTANEOUS		LABOR INDUCED BY PITOCIN		CESAREAN SECTION		TOTAL		INCIDENCE FETAL LOSS OF
	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	INFANTS DELIVERED	DEATHS	
750-999	1	1	3	2	3	3	7	6	85.7
1,000-1,499	6	3	11	4*	1	0	18	7	38.8
1,500-2,499	37	7	19	3†	7	3§	63	13	20.6
2,500+	571	14	72	2‡	13	1	656	17	2.5
Total	615	25	105	11	24	7	744	43	5.7

*Three dead prior to Pitocin.
†One dead prior to Pitocin.
‡Two hydrocephalic infants.
§Two dead prior to cesarean section; severe abruptio placentae.

Analysis of Causes of Death

In Spontaneous Labor.—

Of the 25 deaths in the spontaneous series, 11 were in premature infants. The mothers of these infants were in labor when admitted to the hospital, and in 4 cases no fetal heart sounds were heard. Two premature infants were lost in breech deliveries, when their heads were trapped. There were 2 sets of premature twins with 3 neonatal deaths. One infant succumbed during labor, and autopsy was nonrevealing. One infant, that weighed 2050 grams, whose mother had eclampsia superimposed on malignant hypertension, died four hours after delivery. The mother, who was first seen by us in a moribund condition, in labor, died shortly after delivery.

The causes of death in the 14 infants who weighed over 2,500 grams and were delivered spontaneously are as follows:

Anomalies incompatible with life		2
Erythroblastosis		1
Faulty management in labor		5
Fetal anoxia due to oversedation	2	
Fetal anoxia resulting from paravertebral block	1	
Traumatic delivery	2	
Intrapartum fetal death in eclampsia		3
(One patient also had premature separation of placenta during labor)		
Antepartum fetal death in hypertension		3
At term	2	
At 36 weeks	1	

It is evident that some of the infant deaths associated with spontaneous labor were due to faulty management and not to the toxemia per se. These included 3 deaths from anoxia due to overzealous treatment of the mother; 2 traumatic deliveries in which cesarean section was indicated for obstetric reasons; and several breech deliveries of premature infants in which the use of a Voorhees' bag, as recommended by Parks and Barter,[11] might have been lifesaving.

In 3 patients with hypertensive cardiovascular disease who had stillborn infants delivered spontaneously, the pregnancy should have been terminated earlier. All three of these mothers received good prenatal care and had been admitted to the hospital for study during the present pregnancy. One refused termination at 34 weeks' gestation, and gave birth to a 3,200 gram stillborn infant at 36 weeks. The other 2 patients were allowed to go to 40 weeks' gestation by date, and were delivered of stillborn infants weighing 3,090 and 4,450 grams, respectively. Fetal heart sounds were present in both these patients one week prior to delivery.

Two of the three eclamptic patients who had intrapartum death of the fetus were in labor on admission, but the third did not go into labor until the second day after admission. This child died as a result of premature separation of the placenta. It probably could have been salvaged by terminating the pregnancy on the first hospital day—but not without definite risk to the mother.

In Pitocin-Induced Labor.—

Among the 105 infants born of mothers whose labor was induced by Pitocin 11 fetal deaths occurred. Four of these infants were dead prior to the use of Pitocin and 2 had anomalies incompatible with life. The circumstances responsible for the remaining 5 deaths were as follows:

1. In a breech delivery, a patient with hypertensive cardiovascular disease gave birth to a stillborn infant that weighed 965 grams. Death was due to a prolapsed cord.

2. A patient with severe pre-eclampsia was delivered by the breech method, the infant weighing 1,130 grams. On the second neonatal day the child died of aspiration pneumonia, confirmed by autopsy.

3. A patient with severe pre-eclampsia gave birth to an 878 gram infant that died in four hours.

4. In a 1,675 gram infant born of a mother with severe pre-eclampsia, the fetal heart sounds disappeared 30 minutes before delivery. No cause for death was found at autopsy.

5. An eclamptic patient who had had 11 convulsions gave birth to a 2,210 gram stillborn infant. Autopsy revealed the cause of death to be multiple small cerebral hemorrhages.

In all 5 of these cases pregnancy was terminated in the interest of the mother, even though the infants were expected to be premature or not viable.

The last two deaths described could have been due either to toxemia or to the Pitocin. In the first case the mother was a 15-year-old primigravida with severe pre-eclampsia who had had no prenatal care. She gave a history of having had headache, edema, nausea and vomiting for two weeks prior to admission. On admission her blood pressure was 170 systolic, 115 diastolic, and the urine gave a 3 plus reaction for albumin. Pitocin was given for three consecutive days, beginning on the sixth hospital day. When the cervix, which was long and closed at the beginning of Pitocin therapy, became favorable, the membranes were ruptured artificially and the patient went into labor. The fetal heart sounds were good until approximately 30 minutes prior to delivery, when they could no longer be heard. The infant, that weighed 1,675 grams, was stillborn, and autopsy failed to reveal the cause of death.

In the second case a 2,210 gram infant was stillborn. The mother, a 27-year-old multigravida, had ten convulsions at home and one convulsion after admission to the hospital. On the third hospital day she received Pitocin intravenously, and the following day the membranes ruptured spontaneously. After another intravenous injection of Pitocin on the fifth day, active labor started. The fetal heart sounds disappeared four hours prior to delivery. Autopsy revealed multiple small cerebral hemorrhages as the cause of death.

In Cesarean Sections.—

Among the 24 infants delivered by cesarean section there were 7 deaths. Two of the mothers had severe abruptio placentae, and no fetal heart sounds were present at the time of operation. The remaining 5 deaths occurred as follows:

1 and 2. A patient in mild pre-eclampsia, with oliguria and abruptio placentae, was delivered of twins that died in the neonatal period. The infants weighed 737 and 832 grams, respectively.

3. A 42-year-old woman, gravida viii, was admitted in heart failure, with hypertensive cardiovascular disease and superimposed toxemia. Section was performed after the heart failure had been corrected and the toxemia controlled. The infant weighed 797 grams and died immediately after birth.

4. This patient had mild pre-eclampsia, and the indication for cesarean section was fetal distress. The infant, that weighed 4,720 grams, was stillborn.

5. An eclamptic patient was delivered of a 1,673 gram infant by cesarean section. Death in the neonatal period was due to hyaline membranes.

Of the 7 fetal deaths that occurred in the group of cases terminated by cesarean section, 6 were apparently in no way attributable to the operation. The one case in which the section was probably a factor was that of an eclamptic mother.

This patient, a 25-year-old multigravida, was admitted in coma with a systolic blood pressure of 210, a diastolic pressure of 120, and 4 plus proteinuria. She was referred from another town and was known to have had a blood pressure of 190/110 four weeks prior to admission. She responded well to conservative treatment, and a cesarean section was done under local anesthesia on the fourth hospital day. This means of termination was selected because of an unfavorable cervix. The infant weighed 1,672 grams and its neonatal death was due to a hyaline membrane. This case, which was seen in 1947, would probably be managed today by intravenous Pitocin, since we prefer a vaginal delivery to cesarean section for a known premature infant.

Relative Merits of Pitocin and Cesarean Section

Once the decision has been made to terminate pregnancy because of toxemia, the methods to be employed must be given careful consideration. When the infant is premature or near term and the cervix unfavorable, the consensus in the past has been that a cesarean section should be done in the interest of both mother and child. We have always felt that cesarean section has little place in the management of toxemia of pregnancy, unless there are obstetric indications. However, we consider that cesarean section is justified under the following exceptional conditions: (1) failure of toxemia to respond to treatment, and (2) the development of oliguria (500 c.c. or less excreted in 24 hours) or anuria in a hydrated patient. Neither of these conditions is common, and the first should be rare if treatment is adequate. Our uncorrected incidence for cesarean section is 3.2 per cent in cases of toxemia, as compared with 2.3 per cent in all deliveries.

Cesarean section, as done in the better hospitals, carries a low maternal mortality even in patients with toxemia and should give a good fetal salvage rate. When the infant is premature, however, fetal salvage is generally not as good with section as with vaginal delivery. Dieckmann[12] has pointed out that in the premature infant born of a toxemic mother, particularly one delivered by cesarean section, a hyaline membrane is a common cause of neonatal death. We do not believe that cesarean section necessarily makes an "obstetric cripple," but it may be a deterrent to future childbearing and may tax the judgment of the obstetrician in future deliveries.

In 1951 we[13] reported on the use of Pitocin as a means of inducing premature labor in patients with toxemia of pregnancy. We began using Pitocin for this purpose by the intramuscular route in 1947, and since 1950 we have given it entirely by the intravenous route. Our technique, which has been described previously, consists essentially in the repeated daily administration of Pitocin until the cervix is favorable for artificial rupture of the membranes, or until the patient goes into labor. As we pointed out, the long, closed, or so-called "unripe" cervix can be converted into a "favorable" cervix by the repeated intravenous administration of Pitocin. Other writers have since reported similar results.[14, 15]

We have now used Pitocin in 32 toxemic patients with premature infants. In 4 of these cases the fetus was known to be dead before the drug was started. The remaining 28 patients were delivered of 29 infants, with 5 fetal deaths—an incidence of 17.2 per cent. Only 2 of the infants lost weighed over 1,500 grams and in both these cases the autopsy findings failed to implicate Pitocin definitely as the cause of death. We have also used Pitocin to terminate pregnancy in 72 patients with toxemia of pregnancy who had infants that weighed more than 2,500 grams. Only 2 infants were lost in this series, and both of these were hydrocephalic.

While the use of Pitocin has been successful in our experience, it is not without danger. There has been one maternal death in this series attributable

to its use. This case was reported in detail before the South Atlantic Association of Obstetricians and Gynecologists in January, 1954.[16] The patient sustained a ruptured uterus from the injudicious use of the drug and died as the result of poor surgical judgment and technique. The infant had hydrocephalus and was stillborn.

Our policy in all cases of toxemia, following the patient's admission to the hospital, is to attempt to classify and stabilize the toxemia. Without observation and treatment for a period of at least 24 to 48 hours we do not believe the condition can be properly evaluated. Pitocin is not administered until this evaluation has been completed, and the average hospital stay prior to delivery by Pitocin has been 7½ days, the longest 30 days. This last case was that of a hypertensive patient who was carried to 35 weeks' gestation by date. She was then delivered of a 1,135 gram female infant after five consecutive days of intravenous Pitocin. The child, who is now 4 years old, is progressing normally.

We believe that the fetal results obtained in the series of toxemic cases terminated by the administration of Pitocin for the induction of labor are comparable or superior to those obtained with other methods of termination.

Conclusion

When termination of pregnancy is indicated because of toxemia, the intravenous use of Pitocin for the induction of labor is a valuable adjunct to the armamentarium of the obstetrician, since it may effect delivery in spite of an uneffaced and undilated cervix with a patient not at term. When properly employed, this method of inducing labor is without increased maternal risk and yields a good fetal salvage. In our opinion it has definite advantages over cesarean section or other methods of inducing labor, particularly when the infant is premature.

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Discussion

DR. C. O. McCORMICK, Indianapolis, Ind.—Dr. Mauzy's prime objective appears to me to be determination of the relative value of the two methods of terminating pregnancy—Pitocin induction and cesarean section—for those toxemic patients who have a long, closed cervix. His discussion also includes the results of spontaneous delivery in 606 cases (80 per cent of his series), including those cases encouraged by amniotomy when the presentation and cervix were favorable.

During the past three or four years we had an increasing experience with Pitocin induction in handling toxemic cases. Our results have been very satisfactory; however, in most cases the condition of the cervix has been more favorable than in Dr. Mauzy's cases. Also, we have not followed his routine of giving but one course of Pituitrin daily; in one case we gave five courses within 72 hours. Our experience, though not as extensive as that of Dr. Mauzy, tends to support his conclusion that the method does have advantages over cesarean section.

A word of caution is in order concerning the potential danger of the method. The essayist reports a maternal death from ruptured uterus. Pitocin administered intravenously without proper precautions can be very dangerous.

In determining the merits of different methods of terminating pregnancy from the viewpoint of fetal salvage, it seems inaccurate to include known antenatal deaths. The author reports 4 such deaths before spontaneous delivery, a similar number before Pitocin induction, and 2 before termination by section.

When all factors in general are taken into account, the outstanding influence upon the mortality of prematures is the baby's weight at birth. This fact suggests the advisability of prolonging gestation as long as it is at all feasible to do so. In a series of 600 prematures, all white, delivered during the five-year period ending July 1, 1952, at Indiana University Medical Center, there were 62 born to toxemic mothers. None weighed less than 1,000 grams, and the mortality rate was 8 per cent. The extension of gestation, particularly in toxemic cases, is best accomplished by good prenatal care. Things being equal, the womb is the best incubator. We now know that toxemia per se has no ill effect on babies who are born alive.

Salvaging the premature infant during the natal period hinges chiefly upon the proper choice of analgesics and anesthetics, a generous episiotomy, and a not unnecessarily delayed and nontraumatic delivery technique.

In our series of 600 premature births, analgesia combined with conduction anesthesia was found to give better fetal salvage than conduction anesthesia alone. In 1952 West and his co-workers reported that they found no special advantage to conduction anesthesia in their series of premature deliveries. Breese, in 1938, reported ether the safest anesthetic—indeed, safer than no anesthetic at all. Greer and Lussky, reporting a series in 1940, showed the mortality among prematures born to mothers without sedatives and anesthetics to be 2½ times that of those born to mothers who had sedatives and anesthetics. In 1940, in an address before this Society, I pointed out the favorable effects of certain general anesthetics upon both mature and premature infants. Babies born under this influence experience less weight loss and regained their birth weight more promptly. I attributed these findings to the fact that the babies were spared birth shock.

Of the general anesthetics, cyclopropane is the most hazardous to both mature and premature infants—according to Bundesen, Potter, and associates, eight to nine times as hazardous as ether. Morphine, especially when combined with other drugs, is definitely contraindicated.

In delivering premature infants, it is well to follow the dictum, "The greater the prematurity, the more generous the episiotomy."

Despite our academic teaching that forceps in general are not applicable to prematurity, the low forceps operation is by far the safest means of effecting vaginal delivery of such infants—even safer than spontaneous delivery. Cesarean section for other than

obstetric reasons does not improve the infant's chances for survival. Some reports, including that of Dr. Mauzy, show a much higher mortality rate for premature babies delivered by this method.

After the delayed cutting of the cord, the first and most inmportant protective measure in the neonatal phase is the ample clearing of the bronchial passages. In addition, aspiration of the stomach is often in order. Both these measures are particularly important when dealing with babies delivered by section.

The premature nursery should be under well-qualified pediatric direction, and the nursing care should be supervised round the clock by specially trained nurses. The routine measures, of course, include withholding feedings for 24 to 72 hours; maintaining the proper heating, oxygen flow, and humidity; gastric gavage; postural drainage; close observation for cyanosis; alertness for needed aspirations; protection against infections; the use of vitamin K; and the prophylactic and therapeutic use of antibiotics in combating respiratory infections. In addition, there should be available such adjuncts as the ability to diagnose within the first 24 hours that now recognized and commonly fatal entity, the asphyxial or hyaline membrane, and to institute immediately following the diagnosis *judicious* oxygenation and extra humidification, skill at performing blood transfusion, and special techniques for supersaturation of moisture, such as the mist therapy, in treating dehyration.

These and other considerations in behalf of the infant will enhance the results of the various methods of terminating pregnancy, such as were discussed by Dr. Mauzy, and will proportionately reduce neonatal mortality.

In proving the practicability of substituting Pitocin drip induction for cesarean section in the termination of pregnancy in the toxemic patient with a long, closed cervix, Dr. Mauzy has made a worth-while contribution.

DR. KENNETH T. MACFARLANE, Montreal, Quebec.—This interesting and thought-provoking paper represents a survey of the fetal results in 733 patients with toxemia of pregnancy seen over a seven-year period. It also presents in some detail the results from the use of Pitocin in the induction of premature labor in the "so-called" unripe cervix. During approximately half of the period under survey the Pitocin was given by the intramuscular route, and the intravenous drip method was employed during the latter half of the period. Careful comparison of the infant results in these cases has been made with the results in what the essayist terms "spontaneous delivery." The latter group includes vaginal deliveries at term, whether spontaneous or not, as well as those cases in which labor was induced at or about term by artificial rupture of the membranes.

Such comparisons are very difficult to make because there are so many variables involved, but the author has shown by his careful study that the use of Pitocin to mature the cervix rapidly has a very definite place in obstetrics, and that the results, even with premature babies under 2,500 grams, justify its continued use.

Some authorities find it difficult to support the use of Pitocin by intravenous infusion for the induction of labor, but it appears inevitable that such a valuable method will become more generally used provided it is carefully administered under constant supervision of the physician and in the presence of real and justifiable indications for termination of pregnancy. To report one maternal fatality from its use in this series is most regrettable, as it clouds the otherwise excellent results, but it does re-emphasize the dangers associated with this powerful drug.

It is of interest to compare the incidence of toxemia in Montreal with that reported by the essayist. In the three hospitals with which I am associated the total admissions in 1953, public and private, were 6,226. Of these admissions 269 patients, or 4.3 per cent, suffered from toxemia of pregnancy. During the decade 1930-1939 the incidence of toxemia at the largest of these three institutions, Royal Victoria Hospital, was 13.5 per cent. We feel that this reduction in the incidence of the disease is largely the result of more careful prenatal management and earlier active treatment of the mild pre-eclamptic pa-

tients. Speculation as to why the North Carolina incidence should be almost twice that of our Montreal Group is intriguing. Is the difference of climatologic, dietary, or social origin? Perhaps Dr. Mauzy can enlighten us on this point.

Since the maintenance of pregnancy is the primary etiological factor in this disease, for want of a more complete knowledge the key to its cure appears to be the judicious and timely interruption of the pregnancy in the interests of both mother and child. When the disease occurs before or just at the age of viability and is severe enough to require interruption, I feel that we should adjust our thinking to terms of maternal salvage and end results only, as the future for such previable infants is, in the main, questionable.

In that appreciable group of cases which occur when the infant is viable, but premature, the management is more complicated, and it is in this group that Dr. Mauzy appears to have made a real contribution.

Prior to the recent surgical advances which have increased the safety of cesarean section, this method of inducing labor in toxemic patients would have surely proved an even greater boon. Twenty years ago we used repeated medical inductions for the same reason, but one hesitated to employ Pituitrin, the best agent then available, because of its pressor effect. Thus surgical forms of induction by bag and bougie were more commonly utilized, but the results were far from satisfactory. These methods have been justifiably discarded except for rare cases.

With the greatly improved techniques in cesarean section the swing to that form of delivery has been noticeable, especially the nonteaching centers, and it becomes more difficult to popularize any form of induction. How often one sees cases in which "the long, closed cervix" is recorded as the indication for abdominal delivery! Although the immediate results in cesarean section are greatly improved, it is my considered opinion that there *are* a great many late complications of the operation which should temper the zest for this form of delivery.

Particularly in cases of toxemia, delivery from below would improve both fetal and maternal results. I concur with the essayist that there is little place for cesarean section in toxemia of pregnancy except for the usual obstetric indications, and I would limit its use otherwise to his first indication—"a toxemia becoming worse in spite of adequate treatment." I do not agree with his second indication—"the oliguric or anuric patient"—as this presents a delicate problem in which the balance may be rapidly made worse by any surgical procedure.

I would like to ask Dr. Mauzy if he has any figures on the parity of his group of toxemia patients, as this is one factor which often swings the balance to cesarean section. I would also like to ask him the average number of Pitocin inductions used to ripen a cervix before rupture of the membranes, and how many were necessary after artificial rupture of membranes to establish labor. Has he had any cases of incoordinate uterine action, with constriction-ring dystocia, occurring during his Pitocin inductions? I have recently had two such cases which ultimately required delivery by cesarean section. Has he any secret means of maintaining patient and family morale during the period of these repeated inductions? Induction of labor for convenience or for strictly medical indications to me presents an obstetric situation which may prove extremely trying to physician and patient alike.

It is perhaps fortunate that this problem does not arise too frequently. Careful analysis of this report shows that in only about 15 per cent of the essayist's group of toxemic patients was Pitocin induction or cesarean section used for that specific indication. It has been the happy experience of all of us to find in toxemic patients, prior to the calculated date of delivery, an effacing, soft cervix which can be considered "inducible" by artificial rupture of membranes.

I believe that Dr. Mauzy will agree with me when I say that, in the interests of both mother and child, these premature deliveries should always be effected under local pudendal block anesthesia.

DR. ROBERT WILLSON, Philadelphia, Pa.—I would like to take issue with Dr. Mauzy on one or two points. As he has indicated, one of the greatest pitfalls in the management of toxemia of pregnancy of all types lies in becoming too much interested in the duration of pregnancy rather than in the severity of the toxemia. When toxemia, regardless of the type, is progressing, it probably is not going to respond to any type of medical therapy we have, and the pregnancy should be terminated, almost regardless of its duration.

The term "toxemia," as we all know, means virtually nothing; because what we call toxemia is a heterogeneous group of signs, some of which are directly related to the current pregnancy, while others are only incidental. It is important, in considering the results of the treatment of toxemia, and particularly the results of inducing labor in toxemia, to break the cases down, if it is possible, into the group with pre-eclampsia and the other group of patients with hypertension—who present an entirely different problem. Patients with pre-eclampsia are usually young primigravidas, in whom we do not want to do cesarean section because they have their whole childbearing period ahead of them. They usually are a little farther advanced in pregnancy than are the patients with severe hypertension who develop a superimposed acute process which calls for interruption of pregnancy. It has been our experience that it is quite easy to induce labor in a patient with pre-eclampsia, regardless of the method that is used. If she has true pre-eclampsia, the cervix is often not what we consider favorable, but at least it is beginning to be prepared. Almost anything that is done, whether it is to give Pitocin intramuscularly or by intravenous drip, or to rupture the membranes, is likely to initiate labor. We do not hesitate to rupture membranes, even despite an unfavorable cervix, in the patients on whom we make a diagnosis of pre-eclampsia, because they almost always go into labor.

On the other hand, we have used the suggested method in a number of patients with hypertension and have given 5, 6, and 7 courses of intravenous Pitocin with little or no effect on the cervix whatsoever. It is interesting that the cases reported in the literature in which Pitocin has been successfully used to induce labor are, for the most part, patients with pre-eclampsia, not patients with hypertension.

I should like to ask Dr. Mauzy whether, in his opinion, it is possible to ripen the cervix in the normal pregnant patient and in the patient with pure hypertension, or whether pre-eclampsia adds something to the ease with which labor can be induced.

DR. LEROY A. CALKINS, Kansas City, Kan.—I would like to ask Dr. Mauzy how long he continues the administration of intravenous Pitocin on each day it is given. I would also like to know whether he has any preference for the morning hours or the evening hours as a time for its administration.

DR. NICHOLSON J. EASTMAN, Baltimore, Md.,—As every obstetrician knows, pre-eclampsia may develop at any time in the latter part of pregnancy—at the twenty-eighth week, at the thirty-fifth week, or at term. If it develops near the twenty-eighth week, it is altogether probable that conditions are unfavorable for the initiation of labor and it is unlikely that spontaneous labor will set in. The cervix is often long, firm, and closed. Accordingly if, because of fulminating pre-eclampsia, it is desirable to terminate pregnancy, a larger proportion of this group around the twenty-eighth week will be subjected to cesarean section. If pre-eclampsia develops around the thirty-fifth week, conditions may be somewhat more favorable for the induction of labor. A certain proportion of these cases may show a softer cervix, and as a consequence the incidence of cesarean section will be lower. Although the spontaneous initiation of labor may still be infrequent, the use of methods to induce labor will be more feasible in this group than in those at the twenty-eighth week. In the group at term, the cervix is usually ready for labor, the incidence of cesarean section will be negligible, and the incidence of spontaneous labor will be high.

As a consequence, in any series of this kind, there will be an inordinately large proportion of very small babies in the cases handled by cesarean section. On the other hand, in cases in which spontaneous delivery occurs, the incidence of very small babies will be negligible and most of the babies will be at term.

In the cesarean section group the incidence of babies under 1,000 grams was 12 per cent; in those at term, it was 1 in 571; and in the middle group given Pitocin, it was 3 per cent. Therefore, in evaluating statistics on the management of pre-eclampsia by cesarean section, by induction of labor, and so forth, it is unjust to charge to cesarean section the high fetal mortality that ensues, because that is the natural result of the large proportion of very small babies among the group handled by cesarean section.

In regard to the induction of labor by intravenous Pitocin, since that method was developed in our clinic by Dr. Hellman, a Fellow of this Association, we wish so much that its uses could be extended and that it would prove successful in no end of complications. It has been our experience, however, that, with the long, closed, firm cervix, the initiation of labor by intravenous Pitocin is often unsuccessful. I am cognizant that many obstetricians are seemingly successful in changing a firm cervix to a soft cervix by giving the drug every day for two or three days. We have tried that in case after case. Sometimes it is successful; sometimes it is not successful, and, in the presence of a fulminating pre-eclampsia, two or three days of valuable time may be lost.

The two points I should like to make, then, are these: although I would not want to urge the extensive employment of cesarean section in pre-eclampsia, nevertheless, for the reasons I have stated, I feel that the operation does have a place in fulminating examples of the disease when the patient is far from term and has a long, closed cervix. In the second place, great optimism about the efficacy of intravenous Pitocin for the induction of labor, on the basis of our experience, is unjustified. I would warn you that, while it will be helpful sometimes, in other instances cesarean section will have to be resorted to after Pitocin induction has failed.

DR. WILLIS BROWN, Little Rock, Ark.—It seemed wise that at least some of us from the so-called "eclamptic belt" rise to discuss this very important problem. As I understand the situation presented by Dr. Mauzy, he is considering the factors surrounding fetal deaths associated with hypertensive disease and with the mystical entity of toxemia of pregnancy.

There are at least three variables. One is the damage or the involvement of the placenta which is an accompaniment of the disease. Another is the method of delivery employed. The third is the time at which the delivery is carried out. Each of these three, I believe, contributes immeasurably to the fetal salvage rate. Dr. Mauzy has assayed to measure the role of the method of delivery. May I suggest that this is only one of the three important variables and, as Dr. Eastman has just commented, is perhaps the least important of these three variables.

When we come to consider the matter of placental involvement in this disease, we are all aware that it is basically dependent on the severity and the chronicity of the disease. In the patient with chronic cardiovascular-renal disease who has the onset of clinical manifestations early in gestation, placental involvement inevitably progresses to fibrosis, senility, infarction, and even abruption, with fetal loss completely dependent of the method of delivery. Not only does the earlier appearance of the disease allow more time for severe placental damage, but it also occurs at a more immature stage in the gestational development and inevitably diminishes fetal salvage. The acute toxemia which occurs late in pregnancy seldom threatens the fetus.

It seems to me, therefore, that fetal salvage will probably be determined more by the percentage distribution of these disease entities within the clinic than by the mechanism employed to terminate pregnancy. At our institution, where we receive indigent patients from the entire state of Arkansas, we have a very high incidence of chronic cardiovascular disease arriving on our doorstep at 28, 30, and 32 weeks of gestation. If

we defer termination of pregnancy, the fetus dies in utero; and if we terminate pregnancy, it dies of premaurity and other complications. One cannot forget, then, the important role played by the character and severity of the disease at the time the patient comes under observation.

Let us not forget that there *are* three variables influencing fetal salvage in toxemia, and that the method of delivery is perhaps the least important of the three.

DR. MAUZY (Closing).—In reply to Dr. McCormick, I would like to say that we pay a great deal of attention to the management of premature deliveries. All of our prematures are delivered under regional anesthesia; episiotomies are done routinely, and forceps may or may not be used. The fact that our premature nursery is well equipped and has excellent, trained personnel may in part account for the good fetal salvage.

Dr. MacFarlane has asked about the parity of our Pitocin-induced cases. Thirty of the infants that weighed over 2,500 grams were born of primigravidas. In the premature group, 22 of the mothers were primigravidas. I cannot explain why our incidence of toxemia is 8.2 per cent and yours is only half of this figure, unless climate, nutrition, economic conditions, and the like are factors in the etiology of toxemia. We had no cases of eclampsia in 1953, and felt that perhaps we might have had some influence in promoting better prenatal care in our surrounding territory. So far this year, however, we have had 3 cases.

Dr. Calkins has asked how long we give the Pitocin. The average number of days is generally two or three, with seven the maximum in this series. We prefer to administer Pitocin in the daytime for a period of six to eight hours. All inductions are carried out in the labor room. If labor fails to occur, the patient is returned to her room for a night's rest. The procedure is repeated on successive days. The morale of the patient is maintained by explaining what we are trying to accomplish and by allowing her family to visit her following the attempts at induction. The patient is under constant supervision while the Pitocin is being administered. A number of the cases in this series came from my own private practice, and I have often sat with them throughout the period of induction. It was this personal observation that convinced me of the merits of this method.

Dr. Willson states that he has not found Pitocin to be of value in patients with hypertensive cardiovascular disease. This has not been our experience. The last case mentioned in the paper was a patient with this condition—a private case of my own. Pitocin was given for four consecutive days. At the beginning the presence of a long and closed cervix was confirmed by vaginal examination. On the fourth day the cervix was found to be soft, 1 cm. in thickness, and easily admitted two fingers. The membranes were ruptured, Pitocin was continued, and a 1,135 gram infant was delivered.

It is my conviction that without the use of Pitocin our incidence of cesarean section for toxemia, particularly in the premature group, would have been markedly increased, and I doubt whether our incidence of survival would have been as good.

CARCINOMA OF THE CERVIX IN NULLIPAROUS AND CELIBATE WOMEN*

JANET E. TOWNE, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Stritch School of Medicine of Loyola University)

ATTEMPTING to clarify the etiological influence of chronic irritative lesions in the production of cervical carcinoma, Gagnon[1] investigated a group of women whose religious status would protect them from the usual causes of such lesions. Over a period of twenty years, with an average annual group representing approximately 13,000 women living in religious seclusion, Gagnon was unable to discover a single case of cervical carcinoma. This report has served to strengthen the already deep conviction among many gynecologists and pathologists that cervical carcinoma is, in some way, associated with the consequences of childbirth.

On the basis of the most accurate available statistics on this question, Raymond Pearl[2] has estimated that of 100 American women, about 70 are parous and 30 nonparous; in other words, the ratio is 2⅓ to 1. With due correction made on this basis, however, cervical carcinoma is approximately eight times more frequent in parous than in nonparous women. This would indicate that pregnancy and labor with their attendant cervical trauma bear a causal relationship to cervical carcinoma. Although the reasons for such a correlation are not fully understood, there is a suspicion that infections, chronic irritation, and hormonal imbalance are of considerable importance.

If the role of pregnancies in carcinogenesis of the cervix is of etiological significance, then other variables connected with marriage or sexual congress must be partially associated as causative agents in the nonparous group of patients. If such a partial correlation exists, Gagnon's report of the immunity of celibate women to cervical cancer would establish a relationship between this malignancy and a given factor.

Collection of Data; Statistical Analysis

In order to establish a similar etiological comparison as suggested by Gagnon, a series of known cases of carcinoma of the cervix was reviewed from the records of the Mercy Hospital Institute of Radiation Therapy. During a twenty-one-year period from Jan. 1, 1933, to Dec. 31, 1953, a total of 574 patients with proved primary cervical malignancy was treated. Excluded from this series were those patients who had received various types of original therapy elsewhere, so that the variables of stump carcinoma, recurrences, inadequate treatment, and possible mistaken tissue diagnosis might be avoided.

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

TABLE I. COMPARISON OF CANCER SERIES AS TO PARITY

	NUMBER	PER CENT
Total number of patients	574	100
Pregnancies	480	83.4
Uniparous	101	17.9
Two or more	379	65.73
No pregnancies	94	16.3

Table I merely lends support to the contention that the majority of cases of cervical cancer occur in parous women. In this series 83.4 per cent of the patients were parous.

Since cervical malignancy is seen to be predominantly a disease of the parous woman, can there be other factors connected with marital life of possible significance? Lombard[3] emphasizes that multiple variables which may be of etiological importance include early marriage and pregnancy, contraception, separation or divorce, poor obstetrical care, unrepaired lacerations, and abortions. He further states, however, that the reasons for such correlations are not clear.

If there is a strong association between cancer of the cervix and marriage, this would substantiate the rarity of the disease in the virginal woman.

TABLE II. MARITAL STATUS AND PREGNANCY IN SERIES OF CANCER OF CERVIX

	NUMBER	PER CENT
Total number of patients	574	100
Patients with pregnancies	480	83.4
Married—no pregnancies	57	9.9
Unmarried	37	6.4
Nulliparas—Total	94	16.3

Of the 574 patients included in this report, 94, or 16.3 per cent, were nulliparous (Table II). This figure is slightly higher than those reported by other investigators. It is obvious from a review of the literature on the subject of carcinoma of the nulliparous cervix that a general disagreement exists concerning its frequency. In the statistics reported by Healy,[4] Farrar,[5] and Martzloff[6] the nullipara series represented 2.5, 4.0, and 1.77 per cent, respectively.

The wide discrepancies in relative frequency of this disease would tend to reduce the importance of pregnancy, with its consequent postpartum cervicitis, as an etiological factor in cervical cancer.

In our series 37, or 6.4 per cent, were unmarried. This evidence refutes Sourasky's[7] statement that "some continental authorities hold that while carcinomas of the cervix is a disease of married life, pregnancy is not essential." However, with the realization that the unmarried state does not necessarily imply sexual abstinence, further data were sought.

TABLE III. INCIDENCE OF CANCER OF THE CERVIX IN UNMARRIED WOMEN

	NUMBER	PER CENT
Total number of cases	574	100
Unmarried	37	6.4
Religious	3	0.52

Table III illustrates our findings of cervical cancer in 37 unmarried patients. Of this group a further analysis revealed that 3 of the cervical cancer patients were members of religious communities. Although it would appear that a 0.52 per cent incidence is negligible for the entire series, it should create an appreciation of the fact that cancer of the cervix may develop regardless of the mode of living.

TABLE IV. INCIDENCE OF CANCER OF CERVIX AMONG PRIVATE RELIGIOUS PATIENTS OVER A TWENTY-ONE YEAR PERIOD

Religious Sisters—total	3,083
With proved cervical cancer	3

As is shown in Table IV, our medical files revealed that 3,083 nuns were examined during this same twenty-one-year period and this would then represent an incidence of approximately 1 to 1,000 in our private medical clinic. In a clinical comparison of the three known cases in this group, no history of previous surgical trauma was elicited and all were microscopically confirmed as being of the squamous cell variety.

Not content with our own series of cases, we decided to contact several large religious communities in an attempt either to substantiate our own observations or to disallow them. For this study only those convents which could contribute complete medical charts were asked to submit from their records the names and specific diagnoses of all individuals who had or had had cancer. An effort was made to have these reports sufficiently comprehensive to obviate errors in terminology. Certain reports submitted for this study were omitted because accurate pathologic information could not be obtained. The general survey covers a twenty-year period from 1930 through 1950 and incorporates several large communities, the total annual average of which was estimated to be approximately 10,000 adult women.

TABLE V. TWENTY-YEAR SURVEY OF RELIGIOUS COMMUNITIES WITH AVERAGE ANNUAL POPULATION OF 10,000 ADULT WOMEN

Carcinoma of the cervix—total	3
Microscopically confirmed	3
Living	1
Autopsied	2

Thus, the results would appear to be quite different from those of Gagnon, in that 6 nulliparous virginal women were recorded with proved cervical carcinoma, 3 having occurred in our own series of cases and 3 from the general survey.

In the light of this evidence, pregnancy as a contributing factor in the genesis of cervical cancer would seem to be a less important etiological influence. Regardless of the controversy which will undoubtedly arise from such a deduction, the implication of this study should underscore the knowledge that cervical malignancy can arise in women irrespective of virginity or parity.

Another observation by Gagnon, that fundal malignancies occurred about six times as frequently as those of the cervix uteri, was substantiated by this study as illustrated in Tables VI and VII.

TABLE VI. INCIDENCE OF CORPUS AND CERVICAL CANCER (PRIVATE SERIES)

Private series—total	3,083
Corpus cancer	20
Cervical cancer	3

These figures are at variance with those usually quoted, and an inversion of the accepted ratio of cervical to fundal carcinoma occurs in this study, with 6.6 fundal malignancies found for every cervical malignancy. Whether the lack of parity in these nulliparous and virginal women is the decisive influence in effecting this inversion remains speculative.

TABLE VII. INCIDENCE OF CORPUS AND CERVICAL CANCER (GENERAL SERIES)

General annual average	10,000 women
Corpus cancer	33 cases
Cervical cancer	3 cases

The inversion for this group is slightly higher (11:1); the difference may be ascribed to the increase in the number of women studied.

Since this study is a contrast of known nulliparous women, one may conclude from Tables VI and VII that fundal carcinomas have a notably higher incidence among this group of celibate women than do cervical carcinomas.

TABLE VIII. TYPES OF CORPUS AND CERVIX CANCERS

Cervical cancers	6
Squamous cell type	6
Corpus cancers	53
Adenocarcinomas	50
Leiomyosarcomas	1
Adenoacanthoma	2

The types of malignancies, both fundal and cervical, established histologically are compared in Table VIII. All of the cervical cases were of the squamous-cell variety, while those arising in the fundus were predominantly adenocarcinomas.

Comment

For years textbooks and the literature dealing with cervical malignancy have ascribed a causative relationship of chronic cervicitis to cervical cancer. Many authorities have contributed clinical evidence to support such an etiological theory. Phaneuf,[8] in 100 consecutive biopsies of well-advanced cervicitis, found carcinoma in 10 per cent. From similar evidence Davis[9] established the theory that proper treatment of a chronically infected cervix would cause a 90 per cent reduction in cervical carcinoma.

An appreciation of the seriousness of cervicitis as a forerunner of cervical cancer has stimulated a greater effort to render more appropriate and ade-

quate treatment of this entity. Pemberton and Smith,[10] in an analysis of 1,408 women whose cervices were cauterized, reported that not one was known to develop cervical cancer. Likewise Karnaky,[11] adopting conization in the treatment of 5,000 patients with cervicitis, observed a similar absence of cervical carcinoma.

It is hoped that by advocating and employing such therapeutic practices the problems of an earlier cancer detection may be simplified and improved. With this policy we heartily agree.

Although chronic cervicitis may be caused by other etiological factors, it is generally accepted that the most frequent cause is the trauma accompanying parturition. Indeed, Danforth[12] stated that nearly all, if not all, women who bear children suffer some injury to the cervix. DeLee[13] was astonished at the amount of damage which even normal labor caused, and was amazed at the complexity of the injuries. Williams admitted that slight degrees of cervical lacerations must be regarded as an accompaniment of childbirth. Consequently, since most lacerations become infected, the occurrence of cervicitis can almost be considered a usual event in childbearing women.

Several investigators have pointed out that the number of pregnancies does not influence the occurrence of cervical cancer but that the incidence of a single labor is sufficient.

Although Polak[14] estimated that 85 per cent of all women, single or married, have infected cervices, it is generally conceded that the trauma of labor causes the more severe forms of cervicitis.

Now, although we admit the *influence* of coitus, parity, and attendant cervicitis in the production of cervical carcinoma, we do not wish to exaggerate the role of these factors so as to preclude the operation of others. For, as Novak[15] points out, "There is still considerable difference of opinion among gynecologists as to the importance or unimportance of chronic irritative lesions as predisposers to cancer," and Miller[16] has recently published a study in which this danger is minimized. Novak further states, "In my own experience I have . . . been impressed with the fact that a considerable proportion of early cancers . . . have been noted in cervices showing no noticeable evidence of previous chronic inflammation or irritation."

Novak's remarks are eminently apropos to our investigation. For Gagnon has hypothesized that the lacerations and chronic irritation resulting from the injuries of parturition are *the major factors* in the production of cervical carcinoma. We cannot concur with him, for we have found 6 virginal women with histologically proved cervical malignancy.

While the incidence of cervical carcinoma among this select group of celibate women (6 cases out of 13,083 studied) is admittedly small, yet to disseminate the idea that celibate or nulliparous women never develop cervical malignancies would be erroneous. Such misinformation creates the impression that it is unnecessary to suspect these women of or examine them for carcinoma of the cervix. Also, it might encourage surgeons to continue to perform incomplete hysterectomies on nonchildbearing women, thereby leaving the cervical stump, which has been shown to be more susceptible to the development of carcinoma.

Conclusions

1. Contrary to the results of Gagnon's investigation, carcinoma of the cervix was found to occur in celibate women. Six such cases following a comprehensive survey of approximately 13,000 celibate women were noted.

2. Fundal cancer occurred more often than cervical cancer in the same series of celibate women. In one group of 3,000, the ratio of fundal cancer to cervical was 6.6:1. In another group of 10,000 the ratio was 11:1. These figures are at variance with those usually quoted, and constitute an inversion of the accepted ratio of cervical to fundal malignancies.

3. The operation of etiological factors other than the usual causes of chronic cervicitis in the production of cervical carcinoma is affirmed. The physician is urged to suspect nulliparous and celibate women of cervical carinoma, and to accord them thorough gynecologic examinations.

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Discussion

DR. A. N. ARNESON, St. Louis, Mo.—Dr. Towne's presentation represents another exploration into the intriguing question of environmental factors in cervical cancer. Statistical association with variables involved in marriage is in agreement with data given in other reports, but complexity in those variables makes impossible the specific designation of any single factor or of multiple factors as etiologically significant.

The importance of Dr. Towne's paper is found in the data upon celibate women, and the occurrence of cervical cancer in that group imposes evidence that other influences are involved. In that group, however, Dr. Towne finds inversion of the usual ratio of cervical and endometrial cancer—a finding which presents an interesting question. If the consequences of marriage increase the risk of cervical cancer, does abstinence from those factors result in greater risk of endometrial cancer? Reversal of the usual ratio is to be expected in view of the extremely low incidence of cervical cancer. The probability of endometrial cancer is not known for celibate women, but the 52 cases found by Dr. Towne in reviewing more than 13,000 patients do not appear to represent an unusually high incidence. Since the patients' ages are not given, comparison cannot be made with other data such as the probability values described by Randall for the average population. If there is any deviation from the average, the same alteration should be apparent in breast cancer, in particular, if hormonal effects are of etiological significance.

Mention should be made of an extensive study upon environmental factors in cervical cancer to be reported soon by Dr. Wynder and his co-workers. Data were collected by interviews with patients at American hospitals in New York, Jersey City, Washington, Philadelphia, and St. Louis, and at the Tata Memorial Hospital in Bombay, India. Errors attendant to such a procedure are of considerable magnitude, but the volume of material and the method of analysis are believed to give statistical validity to certain associations. In the attempt to estimate the risk of cervical cancer, they have taken as unity the incidence among women married only one time with the first coitus occurring between the ages of 20 and 24 years. With the first coitus at 16 years, they found the risk doubled. The risk was also found to be approximately doubled for women married two or more times. It is interesting to note that, among all their patients with cervical cancer, only 1 per cent reported no coitus. Among controls without cervical cancer, absence of coitus was reported by 7 per cent of white and 2 per cent of Negro patients. In extending their study, they found the risk of cervical cancer in women exposed only to circumcised males to be only 40 per cent that incurred by women married to uncircumcised husbands.

Whatever the effect of marriage, importance must be given Dr. Towne's affirmation of etiological influences other than the usual causes of cervicitis. The truly infected cervix has been seen only occasionally for some years past. It can also be concluded that the treatment of chronic cervicitis is more effective and more frequently employed. Since the incidence of severe forms is less and the treatment of all forms is improved, there should be a fall in the incidence of cervical cancer if cervicitis is a significant factor in etiology. Improvement in cervical hygiene spans a period that should be adequate for those effects to be noted.

Researchers have accumulated a vast amount of data upon behavior of cells. Histologic recognition of cellular alterations has advanced to the point of transition from benignity to malignancy, but explanation of those changes remains elusive. It is hoped that Dr. Towne will continue her researches, and perhaps correlation may be found between environmental factors and the more incipient stages of cervical cancer. Her current paper is a valuable contribution for its data upon celibate women, as well as for the provocative thought it will produce.

DR. DANIEL G. MORTON, Los Angeles, Calif.—I am actually more intrigued with the substantiation which Dr. Towne's figures afford to Gagnon's findings that cervical cancer is extremely rare in celibate women, than I am with her findings of 6 cervical cancers in 13,000 women in this category. Whatever the explanation, we find here a trail which might well be worth following. We seem to have had demonstrated to us that at least the predisposing causes for cervical cancer can be associated with noncelibacy. When we go further and associate cervical cancer with childbearing, I believe that we are on shakier ground, though of course we all agree that childbearing injures the cervix and subjects it to at least one irritative factor which may be carcinogenic—namely, that of ordinary infection due to the common micro-organisms.

Dr. Towne gives us figures which purport to show that cancer of the cervix is far more common in parous women than in nulliparous. Pearl is quoted as saying that of 100 women about 70 are parous and 30 nonparous, and Dr. Towne goes on to say that, with due correction, cervical cancer is eight times more frequent in parous than in nonparous women. I would like to ask her if this is an entirely satisfactory calculation. In order for such figures to be significant, it seems to me that the age factor must be considered. What we need to know is the relative proportion of parous and nulliparous women at about the age of 45, in relation to the incidence of cervical cancer. Certainly a much larger proportion of nulliparous than of parous women fall into the younger, or low cancer-incidence age group.

A very interesting finding is the relatively high incidence of fundal carcinoma when compared with that of cervical cancer in these celibate women. In this connection we are all familiar with a similar reversal of the usual ratio between these two conditions in

women in the higher income brackets, as compared with those in poor economic circumstances. At least, it can be said that the same factors do not seem to be responsible for fundal cancer and cervical cancer, though they occur in the same organ.

This whole general thesis is an extremely interesting one, and while I think that Dr. Towne's point, that celibacy is no guarantee of immunity to cervical cancer, is very well taken, I am sure that she has no wish to detract from the fascinating implication that cervical changes of some sort, incident to "noncelibacy," may indeed be carcinogenic. In this regard, we have been intrigued by the thought that virus infections of the cervix, about which we know nothing at all, might possibly play a role. It is entirely possible that such infections may exist without producing the usual clinical evidences of inflammation. In any event, I do believe that this is a line of investigation, at present insufficiently explored, which should be pursued.

DR. J. BAY JACOBS, Washington, D. C.—I have had very little experience with cervical carcinoma, but remember that when this subject was presented before the Association quite a few years ago, Dr. James R. Goodall of Montreal commented to me privately that if the cervix is properly treated post partum one is not likely to see any cases of cervical carcinoma. I have always been of the same opinion and was quite pleased to hear his expression, since he was one of the old masters whom we all respected very highly. I have always made it a practice to cauterize any cervix that did not appear perfectly normal, six, eight, or ten weeks post partum, and then to follow up that patient until the cervix did appear normal; and I have never seen a case of cervical carcinoma in my own practice. Treating the cervix post partum will eradicate much of this malady.

DR. TOWNE (Closing).—I am sorry not to have included the age incidence in this group, but it was a hard enough task to select all of these patients and to review what records I could obtain from the communities. Perhaps at a later date it might be done. I realize the importance of the age grouping.

The controversial factors rotate around the importance of examination for all women, regardless of parity or virginity, and I do not believe that we should continue to ask the women to remain celibate. Although Ayre and others have published interesting studies which suggest that such trigger mechanisms as vitamin B deficiency in association with an excess of estrogens may be the decisive influence, other authors have denied that enzymes, viruses, or constitutional states are of clinical significance. In fact, the problem remains unsolved. We have yet to explain the absence, or rather the relative infrequency, of squamous cell carcinoma among the Moslem or Jewish women, who certainly are exposed to the same trauma of childbearing.

HABITUAL ABORTION: HORMONAL PHYSIOLOGY AND A SUGGESTED ENDOCRINE TREATMENT FOR SELECTED PATIENTS*

ROBERT B. WILSON, M.D., ROCHESTER, MINN.

(From the Section of Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation†)

THE causes of abortion that have been described in the literature are numerous. Among them are dietary and vitamin deficiencies, uterine anomalies, malpositions of the uterus, premature separation of the placenta, placenta previa, histaminase deficiency, hemorrhagic diastheses, pathologic ova, incompetency of the internal cervical os, lowered metabolism, psychosomatic abnormalities, and various abnormalities in the metabolism of estrogen, progesterone, and chorionic gonadotropin.[1-20]

In view of the multiplicity of possible causes of abortion it is surprising that there are so many women who conceive and do not abort. It is not surprising that there is little unanimity of opinion as to the proper clinical management of the patient who repeatedly aborts. Most obstetricians, however, do agree on the importance of correcting dietary, vitamin, hygienic, and emotional abnormalities, as well as correcting, in so far as possible, any systemic disease or genital defect. The host of articles describing therapeutic programs employing various endocrine preparations, however, indicates the great diversity of opinion as to the efficacy of such treatment. This diversity of opinion is well exemplified by the reports of the Smiths[16-20] on their treatment of abortion with diethylstilbestrol and the contrary results obtained by Ferguson[21] and also by Dieckmann and co-workers.[22] Furthermore, as King[23] has emphasized, the evaluation of any therapeutic agent or program is relatively impossible because of the improbability that any clinic or person could treat a sufficient number of patients to be statistically significant. Notwithstanding King's statement, the high degree of success obtained in the present series of 6 repeated aborters suggests that there may be a cause-and-effect relationship worthy of further study.

As the computations of Malpas[24] and of Eastman[25] have indicated the increased probability of abortion in women who have had at least 3 consecutive abortions, the patients here reported on were chosen purposely because they had had at least this number of abortions. This presentation is not offered as proof that the endocrine preparations administered were responsible for the results obtained but simply as a report of the results in 6 patients who met these criteria of repeated abortion and who were treated with a natural estrogen and progesterone by mouth, and with chorionic gonadotropin given intramuscularly.

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*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

†The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

The pattern of urinary excretion of the estrogens (estradiol, estrone, and estriol), pregnanediol, and chorionic gonadotropin during pregnancy has been well established.[26-28] The relatively gradual rise in excretion of estrogen and pregnanediol from the onset of pregnancy until term is familiar, as are the sudden rise and equally sudden fall in excretion of chorionic gonadotropin at about the sixtieth to the sixty-fifth day of gestation with a continuing excretion of this substance at a relatively low level throughout the remainder of pregnancy. The function of the estrogens and progesterone in the production and maintenance of the decidua is well known. Fried and Rakoff,[29] Brown and co-workers,[30, 31] and Segaloff and co-workers[32] have recently re-emphasized the luteotropic function of chorionic gonadotropin.

Guterman,[4, 5] and Delfs and Jones,[33, 34] among others, have, by carefully controlled assays, demonstrated an endocrine deficiency or imbalance in patients who subsequently abort. Birnberg and co-workers[35] and Kurzrok[36] have used prolactin (luteotropin) in the treatment of habitual abortion. Fried and Rakoff,[29] Brown and Bradbury,[30] and others[37, 38] have suggested the use of chorionic gonadotropin for these patients. Hamblen,[39] Kurzrok[36] and Kurzrok and Birnberg[40] have used chorionic gonadotropin in combination with other endocrine substances. Rosenfeld[41] and also Hunt[42] have used, because of its content of chorionic gonadotropin, the blood serum of pregnant women. Sommerville and co-workers,[43] Davis and Fugo[44, 45] and Pearlman and co-workers[46] have shown, as far as the estrogens and progesterone are concerned, that while one may potentiate the effects of the other there is no evidence that either can replace the other in the endocrine physiology of pregnancy.

This knowledge of the physiology of the estrogens, progesterone, and chorionic gonadotropin during pregnancy makes it logical to assume that the administration of all of them might be beneficial in patients who repeatedly abort. This opinion is based on the theory that abortions in some patients may be due to an insufficient quantity, lack of quality, or faulty metabolism of these hormones.

Therapeutic Program

The endocrine therapy used in the present series of patients consisted of the oral administration of conjugated estrogens (equine), anhydrohydroxyprogesterone or orally absorbed progesterone or both, and the intramuscular administration of chorionic gonadotropin.* A natural estrogen was used by preference as it seems logical to assume that such an estrogen is more likely to enter properly into normal physiologic and metabolic processes than is an estrogen like stilbestrol which is unallied chemically to the natural estrogens. Progesterone was given by mouth in all except one case. The dosage of this preparation was usually relatively low as it was felt that, if the theory behind the use of chorionic gonadotropin was correct, the addition of large amounts of exogenous progesterone would be unnecessary. Chorionic gonadotropin was used because of its known luteotropic effect. In order to rule out drug sensitivity, a small initial dose of 1,000 I.U. of chorionic gonadotropin was given intramuscularly to all patients. There were no systemic reactions in any case and no patient ex-

*Pranone (Schering).
Premarin, Progesterone Lingusorbs, A.P.L. (Ayerst).

perienced local reactions of any consequence. Following the test dose of chorionic gonadotropin the dosage was then rapidly increased to 4,000 I.U. every other day.

As mentioned previously, the dosage levels of these endocrine preparations may be considered low in view of what is known about the physiology, metabolism, and excretion of these substances. If, however, one takes into consideration the fact that exogenous therapy is, in most instances, supplementary and is not intended to replace completely the endogenous hormones, the dosages selected seem more rational. Furthermore, as far as chorionic gonadotropin is concerned, Leach, Tokuyama, and Maddock[47] have recently shown that the administration of 5,000 I.U. of this hormone to men twice a week will maintain a blood level of this substance comparable to the level found in the blood of pregnant women during the last half of pregnancy. All endocrine therapy was started as soon as possible after the first missed menstrual period and was continued well into the third trimester.

It is to be noted that, in all but one of these cases, there were no clinical signs of threatened abortion. This treatment is thought not to be indicated unless the very earliest stages of pregnancy are clinically normal.

Conventional measures were not neglected. Diets were evaluated, vitamin and iron preparations prescribed, coitus was interdicted, and adequate rest advised. No patient required sedation because of uterine contractions.

Report of Cases

In the following case reports negative ancillary data have been omitted. All patients were healty white women with essentially negative family, medical, and surgical histories. Menstrual function was normal except where noted. There were no clinical or laboratory evidences of systemic or pelvic disease. Serologic reactions for syphilis were negative in all cases. Basal metabolic rates were on the plus side of zero except where noted.

CASE 1.—A healthy white woman, aged 23 years at the time of her first visit to the Mayo Clinic in 1943, experienced six spontaneous abortions from February, 1945, through February, 1949. During four of these pregnancies (2, 4, 5, and 6) various combinations of stilbestrol and anhydrohydroxyprogesterone were employed. The second pregnancy terminated in abortion at 5½ months but the others ended at 2½ to 3 months.

During the seventh pregnancy the patient was treated with conjugated estrogens, desiccated thyroid, and chorionic gonadotropin. The last menstrual period began Dec. 9, 1950, and the expected date of confinement was Sept. 16, 1951. Administration of the endocrine preparations was started 4 weeks after the first missed menstrual period (see Table I). The greatest amount of estrogen administered orally was 3.75 mg. a day; the gonadotropin was given in a dosage of 4,000 I.U. every other day through the fifth month and once a week from the fifth to the seventh months when its use was discontinued.

On Sept. 5, 1951, in the thirty-eighth week of gestation, a normal male infant that weighed 3,160 grams was delivered by cesarean section. The section was done because of a contracted pelvis with failure of engagement of the presenting vertex after a twelve-hour trial of labor. There have been no subsequent pregnancies.

CASE 2.—A healthy white woman was 21 years old at the time of her first clinic visit in 1938. A complete infertility examination was conducted in 1941. In 1946 the first pregnancy occurred and ended prematurely during the thirty-third week of gestation. The premature infant weighed 2,190 grams, was normal, and lived. Three more pregnancies ended in abortion at 4½ to 5 months, the last of the three occurring in 1950. Estrogen and progesterone were employed in the third and fourth pregnancies as shown in the table.

The fifth pregnancy began in 1951. The last menstrual period began July 13, 1951, and the expected date of confinement was April 20, 1952. Two weeks after the first missed period, therapy with conjugated estrogens, progesterone by mouth, and chorionic gonadotropin was

started. By the fifth month, the time of her previous abortions, the patient was receiving 15 mg. of estrogen orally each day, 200 mg. of progesterone each day, and 5,000 I.U. of chorionic gonadotropin every other day (see Table I). These medications were continued until the thirty-seventh week of gestation. In addition to routine measures this patient elected to remain in bed most of the time and performed almost no physical activity. The pregnancy ended uneventfully at the thirth-eighth week with the delivery of a 3,560 gram infant. Except for pyloric stenosis, which was corrected surgically, there were no fetal abnormalities. There have been no subsequent pregnancies. The urinary levels of estrogen, pregnanediol, and chorionic gonadotropin for the last pregnancy are shown in Fig. 1.

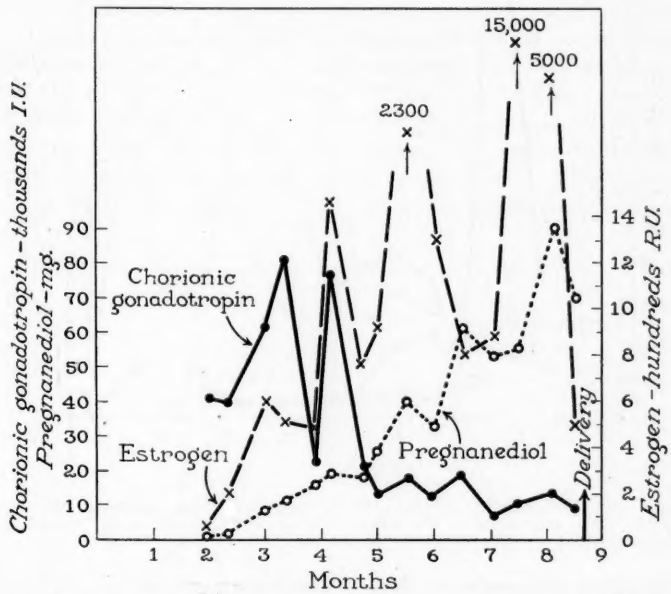

Fig. 1.—(Case 2) At the second month there was no excretion of pregnanediol; 3 weeks later there was but 2.6 mg. in 24 hours. In the fourth and fifth months the amount of estrogen excreted dropped to 770 and 930 rat units shortly after the excretion of chorionic gonadotropin increased to 77,500 I.U. The drop in estrogen excretion at 6½ to 7 months was not accompanied by any change from the normal excretion pattern of chorionic gonadotropin and pregnanediol.

CASE 3.—This patient was first seen during her first pregnancy in 1942, when she was 21 years old. The pregnancy progressed uneventfully and ended at term with the delivery of a 3,150 gram infant. From 1949 to 1951, three spontaneous abortions occurred at 2 to 2½ months. During the third pregnancy 25 mg. of stilbestrol and 30 mg. of anhydrohydroxyprogesterone were given daily. This therapy was not started until after the onset of symptoms characteristic of threatened abortion. This abortion was incomplete and required dilatation and curettage.

The fifth pregnancy began in 1951. The last menstrual period began Dec. 12, 1951, and the expected date of confinement was Sept. 19, 1952. Two weeks after the first missed period, endocrine therapy was started (see Table I). A normal 3,670 gram infant was delivered on Oct. 3, 1952, two weeks past the expected date of confinement. The administration of chorionic gonadotropin had been discontinued at the thirty-first week of gestation and the estrogen and progesterone at the thirty-eighth week. The urinary assay levels are given in Fig. 2.

CASE 4.—This patient made her first clinic visit in 1949 at the age of 29. Three spontaneous abortions had occurred in the period from 1944 to 1948, at 2½, 5, and 2 months, respectively. The fourth pregnancy occurred in 1949. In spite of endocrine therapy another spontaneous abortion occurred at 2½ months. The patient was then unable to conceive. An infertility examination in 1952 gave negative results except for some abnormalities of the husband's semen.

The fifth pregnancy began in 1952. The last menstrual period began Oct. 30, 1952, and the expected date of confinement was Aug. 6, 1953. Three weeks after the first missed period, therapy with conjugated estrogens, progesterone, and chorionic gonadotropin was

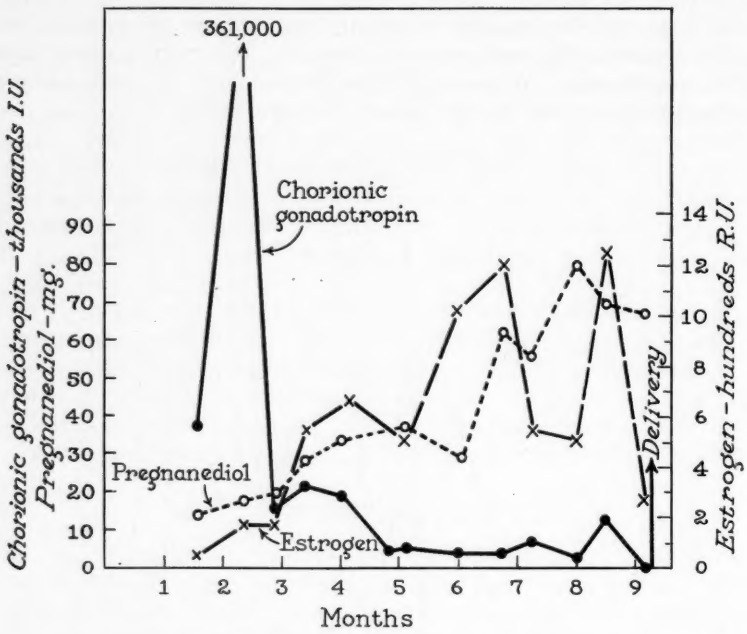

Fig. 2.—(Case 3) Essentially normal hormonal excretion pattern for chorionic gonadotropin, pregnanediol, and estrogen. No chorionic gonadotropin was found in the 24-hour specimen of urine obtained 4 days before delivery.

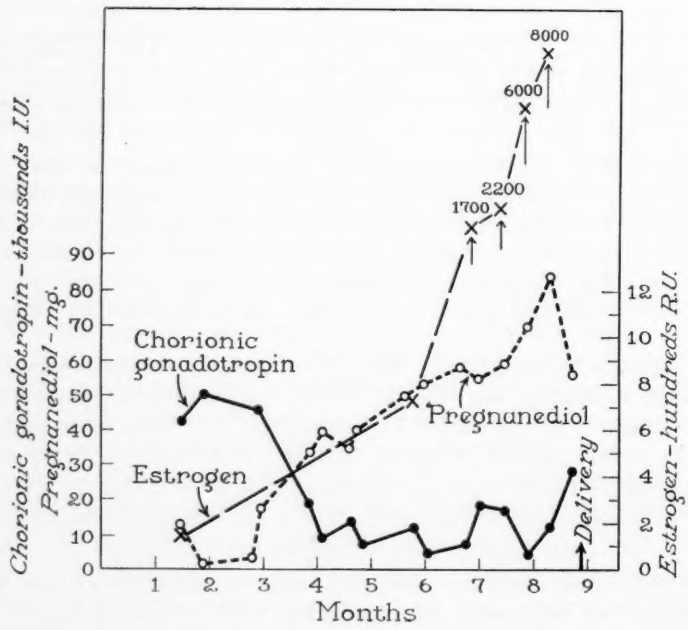

Fig. 3.—(Case 4) Low pregnanediol levels of 2.8 and 3.4 mg. in 24 hours were noted in the second and third months. The peak usually observed in the excretion of chorionic gonadotropin was not obtained in this case.

started (Table I). For approximately 6 weeks intermittent brownish to red vaginal bleeding occurred. Otherwise the pregnancy progressed uneventfully. Use of the endocrine preparations was discontinued at the thirty-seventh week. At 39 weeks, after an uneventful labor, a normal 2,530 gram infant was delivered. The urinary assay levels are shown in Fig. 3. There have been no subsequent pregnancies.

CASE 5.—This patient, in 1951, at the age of 25, experienced three spontaneous abortions. All occurred at the second month of gestation. Because of scanty, irregular menstrual flow, cyclic treatment with estrogen and progesterone was started in February, 1952, and was continued for several months.

The fourth pregnancy occurred in 1952. The last menstrual period began July 11, 1952, and the expected date of confinement was April 18, 1953. Two weeks after the first missed menstrual period, endocrine therapy was started (Table I). The patient had been on a small dose of thyroid, which was continued. The administration of gonadotropin was discontinued at the thirty-sixth week and the estrogen and progesterone at the thirty-ninth. Because of mild pre-eclampsia, labor was induced at the forty-first week. After an uneventful labor, a normal 3,760 gram infant was delivered. The urinary assay levels are given in Fig. 4.

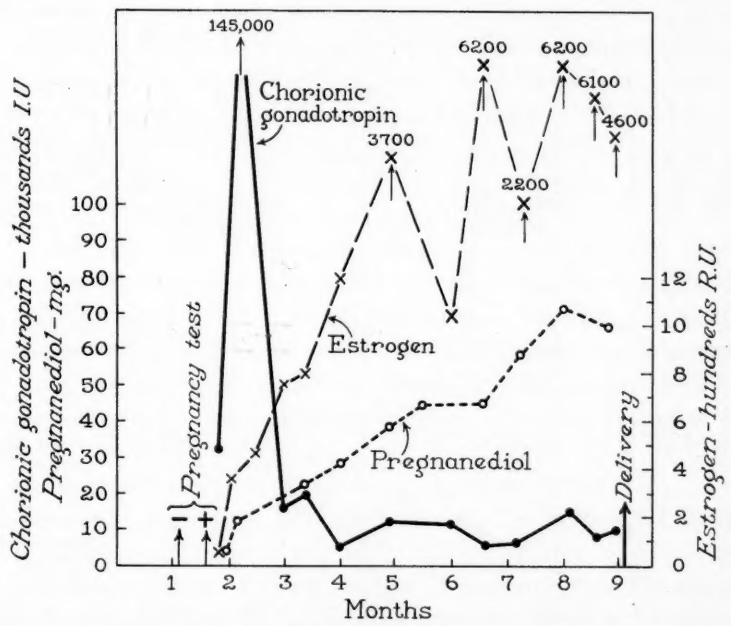

Fig. 4.—(Case 5) The first pregnancy test gave negative results 1 week after an expected but missed menstrual period, indicating a deficiency in the excretion of chorionic gonadotropin. The first value for pregnanediol, obtained in the second month, was low, being 4.3 mg. in 24 hours. The pattern of hormonal excretion in this case was otherwise normal.

This patient recently completed her fifth pregnancy at term. During this pregnancy she received, as far as endocrine therapy is concerned, a maximal dose of conjugated estrogens of 10 mg. per day. Twins were delivered uneventfully. One was normal and lived, while the other died neonatally from atelectasis.

CASE 6.—This patient's first pregnancy occurred in 1949 and ended at term with the delivery of a normal 3,500 gram infant. The pregnancy had been uneventful. From April, 1950, to January, 1953, there were three spontaneous abortions. Stilbestrol therapy was used in the second and third pregnancies. Between these two pregnancies the patient had some menometrorrhagia which was treated elsewhere with thyroid, testosterone, and cyclic stilbestrol.

The fifth pregnancy occurred in 1953. The last menstrual period began July 7, 1953, and the expected date of confinement was April 14, 1954. Two weeks after the first missed period, therapy with conjugated estrogens, progesterone, and chorionic gonadotropin was started (Table I). The patient had been taking 2½ grains of desiccated thyroid a day. With this dosage the basal metabolic rate was plus 1 per cent. Treatment with thyroid was

TABLE I. DATA ON ENDOCRINE TREATMENT IN SIX CASES*

PREGNANCY NO.	PREGNANCY DATE	ESTROGEN. MG. PER DAY	PROGESTERONE MG. PER DAY	THYROID, GRAINS PER DAY	CHORIONIC GONADOTROPIN, I.U.	OUTCOME
Case 1.—						
1	2-45	0	0	0	0	Abortion, 2½ months
2	8-45	1(S)	10-20(AP)	0	0	Abortion, 5½ months, 20 cm. fetus
3	5-46	0	0	0	0	Abortion, 2½ months
4	6-47	3(S)	15(AP)	½	0	Abortion, 2½ months
5	6-48	5-100(S)	150(AP)	0	0	Abortion, 3 months
6	2-49	0	60(AP)	½	0	Abortion, 3 months
7	2-51	2.5-3.75(CE)	0	½	4,000 q. 2-3 days, later once a week	Normal infant, 38 weeks; 3,160 grams
Case 2.—						
1	1946	0	0	0	0	2,190 gram infant, 33 weeks; lived
2	1947	0	0	0	0	Abortion, 4½ months
3	1948	2-50(S)	20-30(AP)	0	0	Abortion, 5 months
4	1950	15-125(S)	0	0	0	Abortion, 5 months
5	1952	2.5-15(CE)	30-100(AP) 100(BP)	0	4,000-5,000 q. other day	3,560 gram infant; normal
Case 3.—						
1	1942	0	0	0	0	Normal infant, 40 weeks; 3,150 grams
2	3-49	0	0	0	0	Abortion, 2½ months
3	9-49	25(S)	30(AP)	0	0	Incomplete abortion, 2½ months; curettage
4	5-51	0	0	0	0	Abortion, 2 months
5	1952	2.5-7.5(CE)	25(BP)	0	4,000 q. other day	Normal infant, 42 weeks; 3,670 grams
Case 4.—						
1	1944	0	0	0	0	Abortion, 2½ months
2	1945	0	0	0	0	Abortion, 5 months
3	1948	0	0	0	0	Abortion, 2 months
4	1949	3-5(S)	20(AP)	1	0	Abortion, 2½ months
5	1953	5-15(CE)	25-50(BP)	0	4,000 q. other day	Normal infant, 39 weeks; 2,530 grams
Case 5.—						
1	1-51	0	0	0	0	Abortion, 2 months
2	6-51	0	0	0	0	Abortion, 2 months
3	12-51	5(S)	20(P)	½	0	Abortion, 2 months
4	1953	3.25-20(CE)	50-75(AP)	½	4,000 q. other day	Normal infant, 41 weeks; 3,760 grams
Case 6.—						
1	1949	0	0	0	0	Normal infant, 41 weeks; 3,500 grams
2	1950	5(S)	0	0	0	Abortion, 2½ months
3	1951	15-50(S)	0	2	0	Abortion, 2 months
4	1953	0	0	2½	0	Abortion, 2½ months
5	1954	5-7.5(CE)	30(AP)	2½	4,000 q. other day	Normal infant, 40 weeks; 3,770 grams

*Abbreviations: AP, anhydrohydroxyprogesterone; BP, buccal progesterone; CE, conjugated estrogens (equine); P, progesterone intramuscularly; S, stilbestrol.

continued. The administration of progesterone by mouth was discontinued at the thirty-first week, the chorionic gonadotropin at the thirty-fifth, and the conjugated estrogens at the thirty-sixth. Mild pre-eclampsia necessitated induction of labor at the fortieth week. A normal 3,770 gram infant was delivered uneventfully. No urinary assays were done in this case.

Comment

The 6 patients comprising this report had had a total of 25 pregnancies prior to the present treatment. These 25 pregnancies had ended with 22 abortions and 3 live births. In 6 subsequent pregnancies, with treatment, 6 normal children were born. This represents complete success in the only patients who have received this treatment.

A rational approach to the endocrine therapy of repeated abortion is most difficult. This is true because multiple endocrine factors appear to be in flux and because of the limits of our knowledge and understanding of the physiology of this physiologic state.

In the 4 patients in whom serial endocrine assays were done, some abnormalities were noted which may be significant. Three of the 4 patients had early pregnanediol levels that were less than 5 mg. in 24 hours. In Case 2, fluctuation in the excretion of estrogen and chorionic gonadotropin is noted to have occurred at the fourth and fifth months of gestation. This abnormality occurred at the time at which the patient had aborted in three previous pregnancies, and the history and the pattern of endocrine excretion are similar to those of a case reported by Randall and Wilson[48] in 1939. In Case 4 (Fig. 3) the levels of pregnanediol were low until the third month; also in this case the assay of chorionic gonadotropin did not reveal the normal peak of excretion that usually occurs in the second and third months. In Case 5 (Fig. 4) it is noteworthy that the first pregnancy test gave negative results, indicating deficient production of chorionic gonadotropin. The usual fluctuations in the excretion of each hormone complex is evident in all patients.

One cannot help being impressed by the frequent endocrine abnormalities found in thoroughly studied patients. Normally we expect that the corpus luteum will produce sufficient estrogen and progesterone to effect a healthy endometrial bed and that the early trophoblast will produce enough chorionic gonadotropin to maintain the corpus luteum until such time as the chorioplacental system produces these endocrine substances in amounts sufficient to maintain pregnancy. When endocrine assays indicate that these conditions do not obtain, there seems to be justification for attempting to correct the condition endocrinologically. The question may then arise as to whether or not these endocrine abnormalities are a cause or a result of abortion. Does a low level of pregnanediol, for instance, indicate deficient production of progesterone by the corpus luteum, faulty metabolism or utilization of this substance, deficiency of the luteotropic chorionic gonadotropin, or any combination thereof?

Inasmuch as this presentation deals with the use of chorionic gonadotropin in the therapy of repeated abortion, it seems worth while to speculate on the possible significance of abnormalities in its excretion. Delfs and Jones[33] have presented the results of assay in 18 patients with low excretion of chorionic

gonadotropin, all of whom aborted. Smith, Albert, and Randall[49] have shown that chorionic gonadotropin most commonly appears in the urine 5 days before the onset of an expected but missed menstrual period, resulting in a positive pregnancy test before the patient has missed a period. These same authors also reported 12 instances in which a positive pregnancy test was shortly followed by abnormal vaginal bleeding and a negative pregnancy test. These findings indicate that chorionic gonadotropin is produced early and that continued production is usually associated with those pregnancies which continue.

It is a not uncommon clinical observation that patients who have been attempting to become pregnant and who have a normal menstrual cycle will have a negative pregnancy test 5 to 7 days after the date of an expected but missed menstrual period. Such patients are often told that they are not pregnant or, if menstruation does not occur within a week or two, to return for another pregnancy test. Apparently physicians overlook the fact that most pregnancy tests are in reality tests for the presence or absence of chorionic gonadotropin. The test used in our laboratory requires at least 30 I.U. per 100 c.c. of urine if it is to be positive. It seems, therefore, that in some patients it would be proper to take the attitude, not that a given pregnancy test is negative and the patient is not pregnant, but that there is present a deficiency of chorionic gonadotropin which might be a cause of early abortion.

An unusual phenomenon is the rapid rise and rapid fall in excretion of chorionic gonadotropin in the second and third months of gestation. Why should this be? Is it because there is a greater number of trophoblastic cells, or because those present are secreting more actively? If one holds to the utilization theory, is there, for some unknown reason, a sudden decrease followed by an equally sudden increase in the utilization of chorionic gonadotropin?

It is strange indeed that so many spontaneous abortions occur at the approximate time of this marked fluctuation in excretion of chorionic gonadotropin. Fluctuations in the excretion of the estrogens and progesterone are also common. Because of this knowledge one is attracted to the theory, and it is only a theory, that these fluctuations could initiate the process of abortion in a uterus which does not readily adapt itself to sudden changes in endocrine environment.

The endocrine treatment of repeated abortions thus becomes rational in theory for certain reasons. First, it may be substitutive in nature, supplying some of the factors necessary for normal environment and growth of the conceptus during time intervals in which there is malfunction of the corpus luteum and of the trophoblast. Second, the administration of exogenous endocrine substances may prevent the initiation of the abortion process in uteri which do not tolerate marked fluctuations in endocrine environment.

It is probably futile to speculate in this manner as it is not possible to state the degree of functional activity of the glands of internal secretion. Knowledge of the metabolism of the various hormones is quite incomplete and speculative. Those who criticize the endocrine treatment of habitual abortion on the basis that it is hit-or-miss treatment perhaps have some justification. On the other hand, in these patients it is not possible to determine in time whether or not an

endocrine deficiency or imbalance is present or will develop; one proceeds with treatment in the hope, and it is only a hope, that the difficulty of the patient under consideration is due to a hormonal deficiency or imbalance and that it can be corrected by the exhibition of endocrine preparations. It must be understood that one cannot determine such deficiency states in time because if one waits until clinical symptoms of threatened abortion appear or abnormal assay results are obtained, then one has waited, at least in some cases, until the optimal time for treatment has disappeared. Furthermore, much has been written to the effect that many abortions are due to defective ova, and it has been indicated that these are not amenable to therapy. It may well be, however, that many of these ova are defective at the time of their recovery, but that they would not be so had their earlier endocrine environment been normal. To me the early treatment of these patients with endocrine preparations is based on the simple concept that, by the use of them, one can assist the woman in her efforts to maintain a normal environment for the normal fertilized ovum. The late treatment is directed toward minimizing the extreme fluctuations of endocrine production.

Summary and Conclusions

Knowledge of the physiology of the estrogens, progesterone and chorionic gonadotropin during pregnancy makes it logical to assume that the administration of all of them might be beneficial in the treatment of patients who repeatedly abort. Consequently, a therapeutic program employing chorionic gonadotropin, a natural estrogen, and progesterone by mouth, in addition to conventional methods, has been outlined, and it has been tried in 6 cases. These 6 patients had had 25 previous pregnancies, 22 of which had ended in abortion. In the 6 pregnancies in which the endocrine therapeutic program was used, 6 normal infants were born. Urinary endocrine assays in 4 patients revealed certain abnormalities which are often seen in patients who abort.

The indicated endocrine treatment should be used before there are clinical signs of threatened abortion. Such treatment is based on the concept that these endocrine substances can assist the human female in her efforts to maintain a normal environment for the normal fertilized ovum and that the extreme fluctuations in endocrine production can be minimized. It is to be realized that the results obtained in this small series may be unrelated to the endocrine therapy employed. Nevertheless, these results warrant further trial of this therapeutic program.

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Discussion

DR. R. A. REIS, Chicago, Ill.—All of us who have an attachment for the history and development of our chosen specialty will have a special interest in the subject under discussion. For habitual or repeated abortion has occupied a place in gynecic literature out of all proportion to its relative importance, and to trace our changing concepts of this problem through the last half-century is fascinating. In 1900 the recommended therapy for habitual abortion was extract of breast tissue. In 1910 this was replaced by desiccated ovarian tissue, in 1920 by aqueous corpus luteum, and in 1925 by desiccated corpus luteum. Vitamin E was the treatment of choice in 1930, progesterone in 1940, estrogen in 1945, and then progesterone and estrogen. Now in 1954 we are told to use a combination of estrogen, progesterone, and chorionic gonadotrophins.

All of these reports have two things in common: the clinical entity of habitual or repeated abortion and the results obtained. Each and every one of the drugs mentioned produced satisfactory results in 78 to 83 per cent of all patients so treated, and for each therapeutic panacea there was unbounded enthusiasm. This continuing level of success makes

one wonder what portion is due to good obstetric care, what portion to good fortune, and what portion, if any, to endocrine therapy. Speert has just shown that 81 per cent of all his habitual aborters were carried to term without benefit of any endocrine therapy. He is convinced, as are many, that hormonal therapy has neither place nor value in the prevention and treatment of habitual abortion.

Today we have a delightful deviation from this pattern, for Dr. Wilson reports 100 per cent success in 6 "selected" patients. I would ask him to tell us how these patients were selected. Also, we should be told just how these 6 fortunate women fit into the over-all picture of repeated abortion in the Mayo Clinic clientele, how many years it took to accumulate these 6 cases, and what happened to all others during this same time interval.

There is considerable evidence accumulating to show that the gloomy calculations of Malpas and Eastman relative to future pregnancies of repeated aborters are mathematically inaccurate. Not being a statistician and being limited in time, I shall not attempt to prove this newer concept here.

Dr. Wilson has used a continuing combination of estrogen, progesterone, and chorionic gonadotrophin. First, I submit that there is still no proof that estrogen actually stimulates steroid production of the placenta. Second, the daily oral dose of the progesterone used was 50 to 100 mg. This is less than one-half the amount which Guterman and others have shown is necessary to change the pregnanediol excretion levels appreciably. Third, I know of no convincing work showing that the administration of the chorionic gonadotrophins available at this time has any effect upon the adult human female.

Fig. 1 shows a low pregnanediol level during the first three months. We have seen many patients with levels this low who did not abort. Furthermore, if the suggested therapy had value, the curve should not have remained low. In Fig. 2 all excretion curves were normal at all times. Why, then, the endocrine therapy?

The author has said that "a rational approach to the endocrine therapy of repeated abortion is most difficult." I submit that in the light of our present knowledge it is impossible. We know too little except that the overwhelming majority of abortions are due to developmental errors or mechanical defects. I repeat my request to Dr. Wilson to tell us how to "select."

It is not my desire to deprecate Dr. Wilson's efforts. I compliment him on his painstaking and time-consuming work, and especially on his efforts toward solving a difficult clinical problem.

In closing—and without changing the subject too much—I wonder what some of our friends in New England will say. Here are 6 patients subjected to extensive and expensive endocrine therapy throughout pregnancy, and yet 2 of the 6 developed toxemia of pregnancy to a degree sufficient to require interruption of pregnancy.

DR. E. STEWART TAYLOR, Denver, Colo.—The prevention and treatment of habitual abortion are receiving increasing attention in many clinics. There is improvement in salvage rates by those individuals who are giving special attention to the problem. Approaches to prevention and treatment continue to be varied. There are essentially two schools of thought: (1) Those who believe that hormone preparations have something to offer, and (2) those who feel that hormones are unnecessary. There is a good deal of evidence to suggest the patients who have early interruptions of pregnancy, late abortions, and premature labor have a coincident low excretion of the hormones of pregnancy. We are doing some work in our own department on the hormonal relationships of premature labor, and have found a tendency toward low excretion of steroid hormone during the pregnancies of individuals who go into labor prematurely. Studying such patients carefully, we are able to show further that the low hormone levels are accompanied by placental insufficiencies, and that the placentas in turn are implanted on a poor endometrium.

Dr. Wilson has carried 6 patients to term after they had had several repeated spontaneous abortions. Most of them had received some type of estrogen and progesterone treatment in previous pregnancies. He has made clinical application of Brown and Bradbury's work of 1947 (Am. J. Obst. & Gynec. 53: 749, 1947). By giving large doses of chorionic gonado-

trophin to normal nonpregnant women, Brown and Bradbury were able to prolong the life of the corpus luteum, produce a decidual endometrium, delay menstruation, and produce a positive biologic test for pregnancy. When the chorionic gonadotrophin was withdrawn, the pseudopregnancy ended, the endometrium shed, and the corpus luteum degenerated. Dr. Wilson has, then, good theoretical and experimental data on which to base his treatment of habitual abortion. Since there are many causes for abortion other than hormonal deficiencies, one must study his patient very carefully for anatomic defects of the uterus, renal disease, and metabolic imbalance. If this is done, one is often able to uncover the cause of repeated abortions. The many articles on habitual abortion emphasize the necessity of preconceptional study with hysterosalpingography, renal function tests, and glucose tolerance tests. It is not helpful to study the steroid hormone excretion previous to the onset of pregnancy. The large problem that all of us face in evaluating the treatment of habitual abortion is our inability to determine in a patient treated with hormones during her pregnancy, what might have been the course if no supplementary hormone preparations had been given. The patient who has had repeated abortions has to be her own control.

To me the works of Mall, Hertig and Rock, and Colvin seem to show quite conclusively that there is no benefit to be derived from hormonal treatment which is started when the clinical signs of threatened abortion are present. Although our knowledge is incomplete and in some places even sketchy, it appears that there is some hope in the preconceptional treatment of abortion and in a treatment as outlined by Dr. Wilson, which is preventive in character.

The following clinical observations may at first appear unrelated to the subject, but I think they are worth mentioning. It has been observed that a patient who has nausea and vomiting of pregnancy, even of the severest type, may be miserable, but she is not likely to lose her pregnancy. We have not seen a patient with hyperemesis gravidarum who has had a spontaneous abortion during that pregnacy. In 1942 Schoeneck (AM. J. OBST. & GYNEC. 43: 309, 1942) demonstrated that there is an increased concentration of chorionic gonadotrophin in the urine of pregnant patients who present symptoms of nausea and vomiting, as compared to patients who are free of these symptoms. Most patients who have a spontaneous abortion have not had nausea and vomiting of pregnancy. A plentiful supply of chorionic gonadotrophin may be necessary to sustain the corpus luteum, which is the source of the estrogen and progesterone for pregnancy during the first 12 to 13 weeks. If chorionic gonadotrophin proves to be helpful in some patients with habitual abortion, it seems reasonable that substitution treatment with estrogen and progesterone would become unnecessary.

Dr. Wilson has had no treatment failures in his series of 6 cases. His results are interesting and impressive. I have enjoyed studying his excellent report, and will look forward to hearing of results obtained during further years of his experience.

DR. J. ROBERT WILLSON, Philadelphia, Pa.—In addition to the usual studies, a patient who has aborted repeatedly should be interviewed and evaluated by a capable psychiatrist. We have recently reported on the psychiatric studies of a group of infertile patients who were emotionally unable to become pregnant. We are now carrying out a similar study on abortions. At the moment it is our thought that occasionally one of these patients will let down her hypothalamic guard and become pregnant. If she is not emotionally able and prepared to stay pregnant and to accept the responsibilities which go with it, she may, by some mechanism with which we are completely unfamiliar, abort.

DR. FREDERICK FALLS, Chicago, Ill.—We were able at the Cook County Hospital with the use of progesterone to change the incidence of salvage in threatened abortion from about 45 per cent to 80 per cent in over 400 patients. At the end of this series, we reverted to the previous treatment of bed rest and sedatives, and found that the salvage rate again fell to 40 to 45 per cent. We feel that progesterone, whether it is supplemented with chorionic gonadotrophic hormone or not, is an important factor in preventing premature labor, as well as abortion.

Our experience has been similar to Dr. Wilson's in the handling of habitual abortion, but I would like to mention one other factor in addition to those that he has discussed, and

that is an anatomic factor. If you examine these women carefully, you will find that a large percentage of them have an arcuate type of bicornate uterus. That this factor may be equally as important as the hormonal imbalance I am thoroughly convinced. Furthermore, the fact that it is an abnormal uterus makes it supersensitive to the stimulation of pregnancy, and therefore increases the likelihood of habitual abortion. By giving an excess of progesterone, you will minimize its ability to respond to this stimulation, and therefore prevent a certain number of these habitual abortions. It is quite simple to demonstrate this deformity on an office examination with a probe inside the uterus. If the point is bent just a little as the probe is inserted, it will go up into a cornu; then on retraction and slight rotation, it will go up into the other cornu.

DR. EDWARD C. HUGHES, Syracuse, N. Y.—We, too, have been interested in this problem for some years—so much so that we established a prepregnancy diagnostic and treatment clinic four years ago. We have studied 125 couples completely during this time, investigating the nutritional, the emotional, the social, the hormonal aspects, and every possible avenue that we could inspect. We have so much material now that we wonder if we'll ever get it together.

There are a few significant findings in this group. Approximately 70 per cent of the patients showed some nutritional deficiencies. Abnormal anatomic development of the uterus has also been found to be present in about half of the patients, which may have been a factor causing premature labor. The vitamin E concentration in the blood has been perfectly normal. Vaginal smears have given us some information, but the condition of the endometrium itself, which has proved to be functionally deficient in about three-fourths of the cases, has been particularly significant. If we appreciate the fact that the chorion, which secretes the chorionic gonadotrophin, must survive upon the endometrium, we must realize that functional failure of the endometrium may result in poor chorion formation, which must affect the development of the embryo very early in gestation.

In patients with bad obstetric histories who aborted following studies early in pregnancy, it was revealed that the excretion of chorionic gonadotrophin was below normal; the peak excretion was arrived at later in gestation than in the normal patient, and the excretion level dropped off rather suddenly. In addition, the pregnanediol excretion in the urine was also below normal. In patients who went into premature labor, the excretion curve of chorionic gonadotrophin followed that seen before abortions. The peak was somewhat higher and occurred at a little later date in gestation, but it fell off rather markedly. In both cases the excretion of pregnanediol in the urine was below normal.

We feel, therefore, that if the chorion fails to develop the embryo suffers, and no matter what endocrine medication you offer, the prognosis for continuing through pregnancy is poor. If, however, chorionic gonadotrophin is given early enough and the excretion levels of chorionic gonadotrophin and pregnanediol are increased, the possibility of carrying the gestation is better. We have given chorionic gonadotrophin in approximately 75 cases. If large doses of chorionic gonadotrophin are given, however—and I mean by that from 4,000 to 10,000 units a day—suppression of the chorion may result, and the amount of chorionic gonadotrophin and pregnanediol excreted in the urine decreases; you might do some harm to such a patient.

We feel that study of these patients before pregnancy is indicated. If pregnancy occurs before preconceptional treatment, the best solution of the problem, taking all other factors into consideration, is the use of chorionic gonadotrophin in moderate doses. Such treatment may improve the fetal salvage in these patients.

DR. WILSON (Closing).—I do not believe there is time to cover more than a few of the questions and criticisms that have been offered.

DR. Reis brought up Speert's report. Speert had, out of 17,500 obstetric patients, 121 with a history of repeated abortion; 81 per cent of these went to term. If the article is read carefully, you will notice that Speert does not include in his series any gynecologic

patients or any patients who had threatened to abort. Therefore his study has to do only with one group of women, and does not give a true picture of the incidence of abortion in women who have previously aborted.

My patients were selected for this treatment, as I think they all should be selected, as a sort of last resort. I am no great enthusiast for endocrine treatment of this kind. It took me about five years to find these 6 cases, maybe it will take me ten years to find another 6. I do not treat very many patients with endocrine preparations during pregnancy. These have been the only ones who have received this particular treatment at our Clinic, and that is all I can say. We have had no failures. Presumably, we have just been extremely fortunate.

As far as dosages are concerned, the doses of Pranone and Premarin were kept low on the theory that the luteotropic action of chorionic gonadotropin would maintain production of endogenous estrogen and progesterone in some degree.

I think Dr. Taylor has quite adequately answered Dr. Reis's criticism that there is no evidence that chorionic gonadotropin has any influence on the adult female. There is a great deal of evidence that this substance has plenty of effect. In that regard, and as is noted in my complete paper, in the August issue of the *Journal of Clinical Endocrinology*, Leach, Tokuyama, and Maddock, who are good investigators, have shown that the injection of only 5,000 international units of chorionic gonadotropin twice a week will maintain, in the blood of men, an amount of chorionic gonadotropin quite comparable to the level of chorionic gonadotropin in the blood of pregnant women during the last part of pregnancy. So the dosage used was not so inadequate as might first appear on the basis of the work of Brown and Bradbury, Segaloff, and Fried and Rakoff.

As far as psychiatry is concerned, I am sure you have all read Javert's articles. Javert, in 1949, reported upon a large series in which the fetal salvage in cases of this type was 86 per cent. In a second series treated with the addition of psychosomatic aids, he recently reported a 90 per cent fetal salvage. Apparently psychiatry is not so helpful as one might think.

As a last word, I would like to add something that I read not long ago, which seems quite applicable to this discussion: "Somewhere between the extreme skepticism both of the very young and of the old and tired, and the transient enthusiasms of the protagonists of this theory or that remedy, lies a middle ground of achievement and even of agreement."

THE CYTOLOGY OF EARLY SQUAMOUS-CELL CARCINOMA OF THE CERVIX*

LOCKE L. MACKENZIE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine)

NONINVASIVE squamous-cell carcinoma of the cervix presents many difficulties in diagnosis. Novak,[1] Te Linde,[2] and many others have written extensively on this subject. To be absolutely sure that no invasion existed, it would virtually be necessary to section serially the entire cervix. In this connection, in 1940, Te Linde and Galvin[3] began to biopsy large numbers of cervices and diagnosed intraepithelial cancer in 109. Subsequent removal of the cervix, which allowed more complete sectioning, resulted in a corrected diagnosis of intraepithelial cancer in only 20, 72 showing invasion, and 16 no remaining malignancy. Many of the 72 showed only glandular invasion.

The greatest value of exfoliative cytology is found in its use as a screening procedure.[7, 23] Suspicious or positive smears must be confirmed by biopsy. Some investigators[4, 5, 6] have described cells peculiar to noninvasive growths, but it is not easy to understand how such cells can be exfoliated from a tumor which does not invade, only to disappear as soon as the same tumor penetrates the stroma. Because it may be very difficult for the pathologist to state with certainty whether a small area is invasive cancer or not, the term "early carcinoma" is used in this paper. This implies carcinoma in situ, or, in two instances, equivocal, minimal invasion. Invasion of the cervical glands without rupture of the basement membrane did not preclude the diagnosis of noninvasive cancer.

The purpose of this paper is to describe the cells and the cytological pattern observed in a series of 27 cases of early squamous-cell carcinoma of the cervix. Secondarily, comments are made concerning previous work in this field. No pregnant women were included, for it is especially difficult to evaluate early malignancy in pregnancy, there seeming at times to be a reversibility from a diseased to a normal cervix after delivery.

Method of Study

When the diagnosis of early carcinoma was made in the biopsy or operative specimen, smears which had been taken beforehand were studied. Large numbers of histological sections were cut in order to rule out invasive cancer or doubtful cases. Smears included both vaginal aspirations, cervical scrapings, and endocervical aspirations; usually the cervical scrapings were the most valuable, a fact pointed out by Ayre[8] and others. Various criteria were considered, and the results tabulated and analyzed. Although the series is small, it is large enough to supply certain data for statistical analysis.

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

Age.—

It is evident from Table I that Wespi's[31] statement that surface carcinoma does not occur after the age of 50 is questionable.

TABLE I. AGE DISTRIBUTION

AUTHOR	NUMBER OF CASES	AVERAGE AGE IN SITU	EXTREMES OF AGE IN SITU	AVERAGE AGE INVASIVE
Te Linde[11]	--	36.0	----	---
Te Linde[3]	75	37.1	24-53	---
Nieburgs[5]	--	40.0	19-72	---
Achenbach[22]	60	35.2	----	48.0
Guin[13]	--	39.5	----	---
Younge[12]	135	38.7	----	61.3
Pund	--	---	23-56	46.0
by biopsy[24]	43	36.6	----	---
by cytology[6]	--	40.0	----	48.6
Mackenzie	27	44.0	32-58	---

Original Diagnosis.—

The original diagnosis was made 24 times by smear and 3 by biopsy. There was preliminary lack of agreement in 5 instances. Three were falsely negative smears in which no definitely malignant cells could be found. Two of these presented marked parabasal-cell dyskaryosis, and the third a decided dyskaryosis of all 3 epithelial layers. In these 3, biopsy and hysterectomy showed carcinoma in situ. Two others were diagnosed as cancer by smears, but as cervicitis by biopsy. Subsequent biopsies confirmed the diagnosis of noninvasive cancer in both. Thus, at the outset, there were 3 false negative smears, and 2 false negative biopsies. It is not the purpose of this paper to contrast methods of diagnosis. Suffice it to quote Daro and his co-workers,[19] "The false negatives of one test were revealed by the positives of the other."

General Characteristics of the Smear.—

Smears are called "clean" or "dirty" depending upon the presence or absence of debris, bacteria, mucus, white blood cells, wandering nuclei, etc. Thirteen cases showed a clean picture, and 14 dirty. Of the entire 27, only 7 presented a pattern typical of menopause. The percentage of cornification was judged in multiples of 10. Cornification was below 30 per cent in 9, and above 40 per cent in 18. The relatively high cornification in this age group is not explained by secondary infection, as cases exhibiting it were equally divided between the clean and dirty smears. Nieburgs and associates[5] noted a high cornification in their series up to the age of 60; after this, it was higher in women with cancer than in those without it. Ayre and Bauld[34] associate high cornification with thiamine deficiency in uterine cancer and in menorrhagia.

The relative abundance of white blood cells, red blood cells, histiocytes, and trichomonads was investigated (Table II). In only one instance were no red blood cells noted. White blood cells were abundant 16 times, and present in smaller numbers 11 times. Large numbers of histiocytes were seen in 9 instances, while they were relatively uncommon in 18.

TABLE II. GENERAL CHARACTERISTICS OF SMEAR (DETAILS)

	ABSENT	FEW	MANY
Red blood cells	1	15	11
White blood cells	0	11	16
Histiocytes	0	18	9
Trichomonads	21	4	2

The relation of trichomoniasis and early cervical cancer has been noted by Papanicolaou,[16] who states, "A high percentage of parasitic infections, chiefly

trichomoniasis, has been noted in such cases.'' In the present series, 6 had this parasite, 21 did not, a percentage of 22. Davis,[25] in a personal communication, gives figures for about 7,600 women who were free of cancer, showing that about 20 per cent had trichomoniasis. Davis also has supplied some significant figures which may tend to show a possible relationship between cancer in the younger age group and this flagellate. He found the average age of 11 women with both cancer of the cervix and trichomoniasis to be under 40, while the average age of 80 women with cancer of the cervix but without the trichomoniasis was over 50. Figures for the series presented in this paper show the average age of 6 women with both diseases to be 41, while 21 with only cervical malignancy averaged 46 years of age.

Suspicious Cells.—

Careful examination under high-power magnification is often necessary to determine whether certain cells are malignant or not. Such cells invariably pose a difficult problem of interpretation, and, because they resemble cancer cells so closely, a special study was made of them. Many fall under the classification known as dyskaryosis, and have a particular significance.

Table III shows the epithelial layer from which such cells originated. Intermediate layer cells, it should be noted, are considered to be characterized by cell borders with acute angles, often smaller than the superficial cells and with a relatively larger nucleus; they generally take a basophilic stain, and are usually irregularly shaped in contradistinction to the flat, polyhedral shape of the superficial layer cells. Such intermediate layer cells include, but are not restricted to, the specialized navicular cells.

TABLE III. SUSPICIOUS CELLS (ORIGIN AND GROUPING)

Superficial layer	5
Intermediate layer	17
Parabasal layer	13
Endocervical	1
Cells tend to occur in groups	13
Cells tend to occur singly	14

Table III also illustrates grouping of these suspicious cells. The next table (Table IV) is a composite to show details of cytoplasm and nuclei in these cells.

TABLE IV. SUSPICIOUS CELLS (DETAILS)

Cytoplasm.—	
Scanty	8
Abundant	19
Nucleus.—	
Usually single	27
Many double	12
Many multinucleate	4
Many giant	7

Cancer Cells.—

It is of primary interest to determine from which epithelial layer the early cancer cells are exfoliated. It is apparent in Table V that the intermediate and parabasal layers were involved most frequently (29 times), while the superficial and endocervical layers were involved only twice. There was a high correlation between the layers from which the suspicious and malignant cells were exfoliated, only one case showing different layers. A well-known criterion of cytological malignancy is the fact that cancer cells appear in groups. Table V illustrates this. It is seen that groups occur over 3 times as often as single cells, a tendency not present in the suspicious cells. Of course, every smear shows both arrangements, and this table depicts only the general trend.

TABLE V. CANCER CELLS (ORIGIN AND GROUPING)

Superficial layer	2
Intermediate layer	15
Parabasal layer	14
Endocervical	2
Cells tend to occur in groups	19
Cells tend to occur singly	5
(no cancer cells seen)	3

No single cell was found which was diagnostic of early cancer of the cervix, although several authors[4, 5, 9, 26, 27, 28] have described cells which they contend are either pathognomonic or highly suggestive of surface carcinoma. All such cells were found in several of the smears studied herein, but none was present in all, and all have been noted in cases of definite invasion. Highly differentiated cells, usually thought to be associated with advanced lesions, such as spindle cells, tadpole cells, bizarrely shaped and vacuolated cells, etc., were seen in 14, or 50 per cent, of this series. Perinuclear vacuoles were noted in 4 instances, an increased perinuclear membrane in 5, and marked irregularity of the nucleus in 19. Frequent multiple nuclei were present in 3 cases. True nucleoli or karyosomes were usually multiple, varying from 2 to 5 in number, but occasionally these occurred in numbers of 8 to 10. The chromatin network was noted as being finely granular in 9, coarsely granular in 13, irregularly grouped in 8, and regularly grouped in 9. Marked hyperchromatism was seen 9 times, and many shadow forms (hypochromatism) 6 times. Nuclei were usually regular in 21 cases, and irregular in 19, some smears showing about equal numbers of both. The cytoplasm was clear in 17 smears, granular in 6, and foamy or vacuolated in 2 each (Table VI).

TABLE VI. CANCER CELLS (DETAILS)

Differentiated (including 7 spindle, 3 tadpole)	17
Undifferentiated	12
Clear cytoplasm	17
Granular cytoplasm	6
Vacuolated cytoplasm	4
Nucleus usually regular	21
Nucleus often irregular	19
Nucleus often multiple	3
Chromatin coarsely granular	13
Chromatin finely granular	9
Chromatin regularly arranged	9
Chromatin irregularly arranged	8
Chromatin hyperchromatic	9
Chromatin hypochromatic	6

In the present series, cancer cells tended to appear in groups, to have a single nucleus, and a granular chromatin.* The cytoplasm was usually clear.† No other observed criteria were statistically significant. The nucleus was almost equally regular or irregular in outline. There was often an increased staining density of the perinuclear membrane, and the chromatin was frequently hyperchromatic.

Comment

It would be of great value if cytologists could describe a cell or cell pattern distinctive of either surface cancer or premalignant change. Reagan[28] states

*Chi square is statistically significant below the 0.01 level.
†Chi square at 0.10 – 0.20 level.

that there are certain cells which are characteristic of carcinoma in situ, but that they are not confined to this lesion alone. In another article[9] he declares that the cell patterns in basal-cell hyperplasia resemble those in preinvasive carcinoma, but the changes are less marked, and there are fewer cells, possibly because of the ability of cancer cells to exfoliate more readily than other cells. He believes the cells described by Ayre as "precancer cells" are more characteristic of hyperplasia. Three cases in this series (Nos. 7, 12, 24) showed the specific cell type described by Nieburgs and Pund[4, 5] near clumps of spindle cells characteristic of more advanced, infiltrating tumors. It was not unusual to note very bizarre cells in slides from women whose lesion was limited to a tiny surface area. The Staff of the Vincent Memorial Hospital,[26] in a review of the cytologic diagnosis of cancer, makes a distinction between differentiated and undifferentiated cells. They state that if only the "third type differentiated

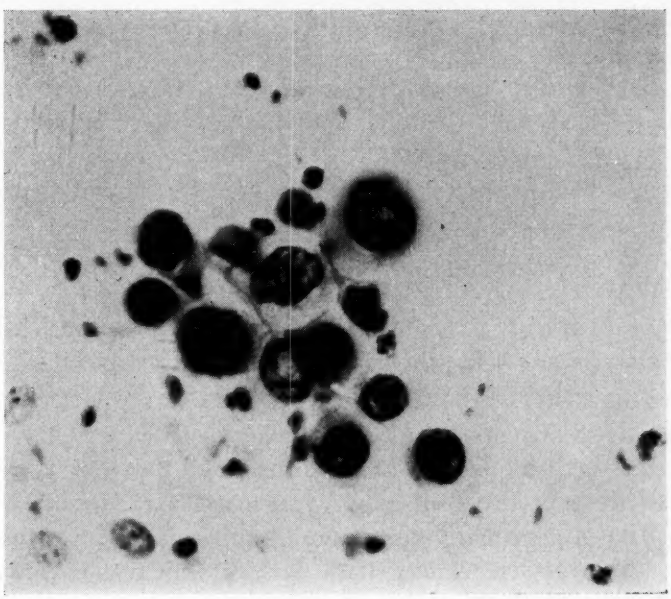

Fig. 1.—A group of third type differentiated cells. Nuclei round or oval. Cell borders distinct. Relatively abundant cytoplasm.

cells" are present, the neoplasm is usually carcinoma in situ. They describe this type of cell as having a sharp border, a wrinkled nucleus, an irregular chromatin network, and an increase in the chromatin content. In the present study, according to the standards of the Boston group, 17 cases showed a majority of the cancer cells to be differentiated, and 12 undifferentiated. Typical third type differentiated cells were seen in 14, or about 50 per cent (Fig. 1). Such cells seemed to arise from the parabasal layer, were found more often singly than in groups, usually looked definitely malignant, and stained brilliantly and deeply with both nuclear and cytoplasmic dyes. The histopathological picture did not always parallel the cytological picture in so far as differentiation is concerned. Thus, in Case 24, a moderate number of highly differentiated cells was associated with an extremely anaplastic tumor.

Gynecological pathologists have recently been much concerned with problems associated with various degrees of hyperactivity of the basal cells of the cervical epithelium, and with the possibility of such lesions developing into a true cancer. Te Linde and Galvin[3, 10, 11] believe such a change may or may not take place, a view shared by Reagan,[9] Wespi,[31] and Galvin, Jones, and Te Linde.[33] Younge and his co-workers[12] report a case which seemed to progress from basal hyperactivity to carcinoma in situ. On the other hand, Novak[7] does not think that hyperactivity is necessarily a precursor of carcinoma in situ, as it may be produced by inflammatory or hormonal activity. Many authors have pointed out the apparent reversibility of these changes, originally noted after parturition. Guin,[13] however, demonstrated that hyperactivity of the basal cells was most often seen in the same area—the squamocolumnar junction—as that from which carcinoma generally arises. She further described an imperceptible merging in the same section of a benign basal-cell hyperactivity with a malignant carcinoma in situ.

Divergent opinions are expressed regarding the exfoliation of cancer cells. Nieburgs, discussing a paper of Pund's and his,[6] says "the pre-invasive carcinoma exfoliates much more rapidly and with a larger number of cells than invasive carcinoma." Achenbach and associates,[22] however, write that "malignant cells occurred with less frequency in cases of preinvasive carcinoma than in those of more advanced cervical tumors, and are often accompanied by abnormal precornified squamous cells with markedly enlarged but otherwise normal nuclei. These atypical anaplastic cells occurred in more than 60 per cent of these cases, although they themselves are considered benign." In the present series, there were 18 cases in which large numbers of cancer cells were found, 6 where few were seen, and 3 in which none could be discovered.

For some years Papanicolaou[14, 15, 16, 29] has been describing dyskaryosis in exfoliated cells from the vagina and uterus, and this has introduced a new concept into the interpretation of cytological material. A smear may not be reported as positive unless malignant cells are present, yet a sizable number of women have early cervical cancer with smears which show only dyskaryosis. In the present series of 27, there were 3 such instances. Spreads showing marked dyskaryosis must be interpreted as suspicious, or Class III, and biopsy should be requested. As Papanicolaou has remarked, such smears need a great deal more study, as they may hold the clue to the earliest malignant changes as seen in exfoliated cells. He also points out[15] that the commonest dyskaryotic pattern is that involving the superficial cells, while the rarest involves the intermediate layer cells. He seems now to have limited his concept of intermediate cells to navicular cells. If basal-cell hyperplasia is truly of significance, and if this lesion is associated with a parabasal-cell dyskaryosis, it seems logical that this type of dyskaryosis would be the most important from the point of view of the subsequent development of malignancy. In his latest publication, Papanicolaou[29] seems to feel that parabasal-cell dyskaryosis and endocervical-cell dyskaryosis are of greater significance than the other types, that they show less tendency to reversibility, and that they are inclined to progress to invasion more rapidly.

TABLE VII. DYSKARYOSIS

Intermediate layer	18
Parabasal layer	10
Superficial layer	6
Endocervical cell	1

Dyskaryosis is also discussed by Reagan,[28] especially the superficial cell layer types. Of the 27 cases detailed in this study (Table VII), 18 showed marked dyskaryotic patterns as follows: 18 intermediate layer; 10 parabasal layer; 6 superficial layer; and 1 endocervical-cell layer. Many presented a combination of various layers. It should be pointed out that some here listed as intermediate layer might have been called superficial layer dyskaryosis by Papanicolaou's present classification.

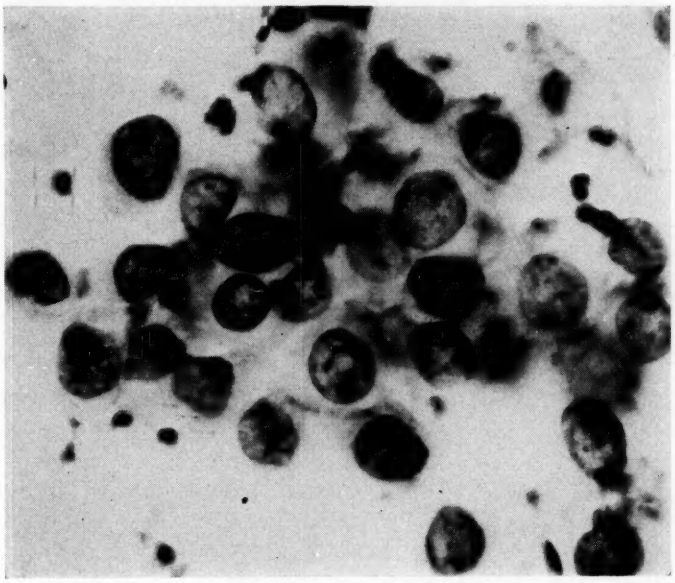

Fig. 2.—Cell pattern of early squamous-cell carcinoma of the cervix in which most of the cancer cells are of the third type differentiated variety.

Much work has already been done to show the relative accuracy of cytological diagnosis in early cancer of the cervix. Hoffman and his co-workers[30] state that "wide use of the vaginal smear has greatly increased the reported total of in situ carcinomas." Fremont-Smith, Graham, and Meigs[17] in 1947 reported 12 carcinomas in situ with positive smears in 10. Reagan[9] found malignant cells in the spreads of 51 of 54 preinvasive cancers of the cervix. Gusberg[18] noted 45 positive smears in 53 cases. Daro and associates[19] reported 41 of 43 cases as positive by smears, although they call these early lesions "intraepithelial metaplasia." Foote and Li[20] stated that 14 of 18 cases showed a positive cytology. Younge and his group[12] found smears to be positive in noninvasive cancer of the cervix in only 52 per cent when the disease was limited strictly to the surface, but in 93 per cent if the cervical glands were involved. When only vaginal—not cervical—smears are examined, the results are very different.

While Achenbach, Johnstone, and Hertig[22] noted that vaginal smears were positive in 82 per cent of their series, Kulcsar[21] found false negative results in 45 per cent of intraepithelial cancers when judged by vaginal smears, but in only 7 per cent when cervical scrapings were included, while Foote and Li[20] in a comparable study of 18 cases give figures of 50 per cent and 12 per cent. It was Ayre[8] in 1947 who urged what he called "selective cytology"—that is, cervical

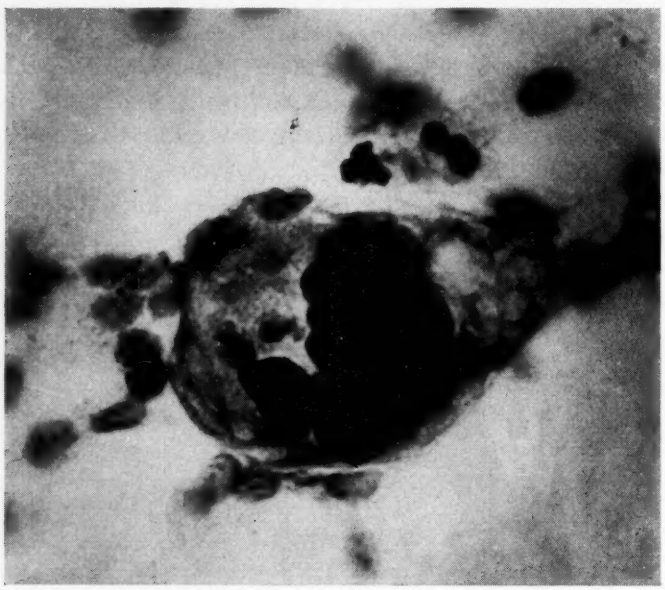

Fig. 3.—Example of bizarre cancer cell seen in certain cases of early squamous-cell cervical cancer.

Fig. 4.—This is the cytological pattern occasionally found in noninvasive carcinoma of the cervix. No malignant cells were found. This is the picture of superficial cell dyskaryo-

scraping—as an aid in the diagnosis of cervical cancer, while the next year Seibels[32] stressed the importance of obtaining cells from all areas of the cervix. In the present series of 27 cases, cancer cells were found in 88 per cent.

This report does not confirm the opinion of various authors[4, 5, 6, 9, 14, 15, 16, 26, 28, 29, 36] in so far as there tends to be a single type of cell or a single cell pattern which is characteristic of noninvasive carcinoma of the cervix. The facts tabulated from this study are in agreement with the conclusions of Schinz and Uehlinger[35] regarding the nonspecificity of a cellular pattern. Three divergent patterns were seen. The first (Fig. 2), noted 15 times, corresponded well with that described by the authors referred to above. Smears showed the "early" malignant cells, arranged in small groups, and there was an absence of the more bizarre cell types. The second was in all respects similar to that seen in advanced cancer, with highly differentiated cells of unusual morphology (Fig. 3) often arranged in large groups; this was seen 9 times. The third pattern presented only a marked dyskaryosis of one or more cell layers with no malignant cells. This type was found 3 times (Fig. 4).

Conclusions

1. The cytological pattern of early squamous-cell carcinoma of the cervix is divided into three distinct types.

2. No single cell or cellular pattern is diagnostic of early squamous-cell carcinoma of the cervix.

3. Early squamous-cell carcinoma of the cervix cannot be differentiated from invasive cancer by cytological means.

Smears and tissue sections were obtained from the New York University Hospital and from Bellevue Hospital, New York University-Bellevue Medical Center, the Methodist Hospital of Brooklyn, the Cancer Control Program of the University of Puerto Rico, and in one instance from the Lenox Hill Hospital in New York City. The author has reviewed all sections and smears, and acknowledges with thanks the assistance of Dr. Maurice Richter, Pathologist to the New York University Hospital, in evaluating certain histopathological sections.

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Discussion

DR. JOHN I. BREWER.—It is always refreshing to hear differences of opinion expressed upon histologic and cytologic material. Dr. Mackenzie disagrees with those who believe that certain cells, if present in the smear, are pathognonomic of an in situ lesion. In his material he was not able to find any cellular change that was specifically and consistently indicative of this lesion.

The changes in the cervical cells which suggest to some investigators that the lesion is solely intraepithelial consist of alterations in the morphology of the nucleus, chiefly in the parabasal type of cells, which still retain their general, normal configuration. It is true, in the experience of Dr. Frank Maher in our laboratory, that when these cell changes alone are present, the lesion *may* be intraepithelial. But this is not an absolute criterion, since in some instances the lesion is invasive, and in others the lesion is not even intraepithelial carcinoma but rather is a hyperplasia or dysplasia, or only an inflammatory reaction. Our experience is similar to that of the essayist, namely, that there is no single type or pattern of cell which provides an absolute distinction between noninvasive and invasive carcinoma.

The attempt to distinguish between noninvasive and invasive carcinoma of the cervix by a study of vaginal or cervical smears is well worth while, for quite obvious reasons. A great deal of effort has been devoted toward this end during the past five years, and some progress has been made. It is now thought by some workers that such a distinction may possibly be made in some instances, whereas at the beginning few considered it possible, or even feasible to make the attempt. Progress has not been made to the extent that the character of the lesion is determined solely from the smear without a study of the tissues obtained by biopsy. The interpretation of the characteristics of an entire lesion by a study of meager changes in a few isolated cells or groups of cells is too treacherous and uncertain, and probably will always remain so. In the same manner, biopsy or the section of a few blocks of tissue from a large tumor which has been removed surgically can never reveal with complete accuracy the exact character of the entire tumor in all instances. It is often surprising what one can learn when the complete tumor is examined microscopically. This fact does not detract from the efforts being made to learn more about the cellular changes in early carcinoma from a purely scientific standpoint, but it should discourage the acceptance of changes observed in smears as sufficient evidence on which to predicate and carry out therapy.

The use of the term "differentiated" by some workers engaged in studies of the vaginal and cervical smears has created confusion; for example, the essayist uses (as do others) the term "highly differentiated" to describe such cells as spindle cells, tadpole cells, and bizarrely shaped and vacuolated cells. To the pathologists the term, by long

and general usage, signifies cells that resemble the large, mature, squamous pavement cells, not such cells as those previously mentioned. It appears that this confusion might well be avoided if the cytologists in this field would use this term in accordance with the general custom. Papanicolaou has said that, while some workers refer to these particular cells in advanced malignancies of the cervix as "differentiated," the term appears to be more fitting for designating the dyskaryotic cell types of early malignancies which still retain the identifying characteristics of the normal type. Even this usage would not clarify the confusion.

The author uses the term ''early carcinoma'' as a synonym for the presently more generally accepted ''carcinoma in situ,'' ''intraepithelial carcinoma,'' ''noninvasive carcinoma,'' or ''surface carcinoma.'' In this way he implies that the lesion is a real carcinoma; in fact, he uses the same term, ''early carcinoma,'' in describing two early invasive lesions. While most will agree that invasive carcinoma has its inception in the intraepithelial lesion, there are many, including myself, who still prefer to reserve the name ''carcinoma'' strictly for the invasive lesion from which there is no spontaneous return. Furthermore, the term ''early carcinoma'' has been used so frequently to designate the small lesions of invasive carcinoma that great confusion will result if a new connotation is given. This last argument alone is a good reason for rejecting its use in the manner the author has chosen.

In the text of the paper the following statement is made: ''It is especially difficult to evaluate early malignancy in pregnancy, there seeming at times to be a reversibility from a diseased to a normal cervix after delivery.'' Since the author does not mention the fact that there is another side to this particular question, the impression is left with the reader that there is no other side. Nevertheless, the work of Greene and the group at Northwestern, and of Hamperl, Kaufmann, and Ober quite definitely indicates that this statement should not be accepted as a fact without a great deal more evidence, and that in all probability the reverse is true.

There is one statement made in the paper which, while true and accurately quoted, leads to quite an erroneous conclusion. If it remains unchallenged, further confusion and misquoting will result. This is the quotation from an article by Te Linde and Galvin to the effect that, of 109 lesions diagnosed as intraepithelial, 72 showed invasion when the cervix was removed and studied. These authors actually did say this, but in subsequent articles they clarified their use of the term ''invasion.'' In the quoted article the term ''invasion'' was used to connote extension into glands as well as actual extension into the stroma. With more work and more solidification of thinking with respect to the real significance of projection of the epithelium into the glands, Te Linde and Galvin have revised their use of the term ''invasion'' and now make a distinction between gland extension and stromal invasion. Since they have made this correction, I believe that their more recent statements should be used and this quotation of their previous work should be discontinued. True tissue invasion is not nearly as frequent as their old figures would indicate. The following statement made by Te Linde in a personal communication to me may answer, once and for all, this preceding and frequently debated statement of theirs: ''In fact we did use the term 'invasion' indicating a 'glandular invasion.' There obviously is a distinction, which we have made in subsequent articles. It is true that we found carcinoma beneath the surface in 72 of 109 cases but, in many of these, this was simply glandular involvement.''

Some day it may be possible to differentiate between noninvasive and invasive carcinoma with absolute accuracy by vaginal-smear studies. Until then, we shall have to review the evidence as presented, such as that heard here today, and make our own decision. On the basis of our own studies we are in accord with the author's conclusions that it cannot be done with complete accuracy at this time by cytology alone.

DR. F. BAYARD CARTER, Durham, N. C.—The interpretation of intraepithelial carcinoma is not only a challenge in cellular morphologic differentiation but also is a fascinating problem in cytologic prognostication. The result is gratifying when the cytologist's evaluation of cellular atypism is verified by the histopathologist.

During the past seven and one-half years of our program in cancer control, 242 intraepithelial carcinomas of the cervix have been diagnosed by histopathologic studies. Genital

smears were obtained from each patient concerned. In the course of our work several papers have been written concerning the problems in the cytologic recognition of intraepithelial cervical carcinoma. Two papers, based on 112 and 151 cases, respectively, published by our group in 1952, have covered the salient points in Dr. Mackenzie's paper. Early in our studies it was recognized that the aberrant forms in cytologic preparations often were essentially the same in patients with squamous-cell carcinoma as in those with intraepithelial carcinoma. In other cases they were entirely different, and in others still, they overlapped. As a result of these findings, a detailed system of classification was instituted in order to identify more specifically degrees of abnormality in which *nuclear variation was of primary concern.* The classification is shown in Table I.

TABLE I. CLASSIFICATION OF GENITAL SMEARS—FEMALE

Type I.	Epithelial elements apparently normal
Type II.	Abnormal but benign cellular changes
	(A) Like Type II, but including slightly atypical nuclear irregularities
	(B) Includes elements characterizing Types II and IIA with addition of greater cytologic atypicalities
Type III.	Atypism comparable with noninvasive carcinoma. Also, questionable malignancy
	(A) Questionable intraepithelial carcinoma
	(B) Intraepithelial carcinoma
	(C) Intraepithelial carcinoma, or may be invasive
	(D) Questionable malignant cells
Type IV.	Elements present thought to be malignant tumor cells; scarce
Type V.	Elements present thought to be malignant tumor cells; abundant
	(A) Squamous-cell carcinoma, cervix; may be only intraepithelial carcinoma
	(B) Malignancy

TABLE II. CLASSIFICATION OF INTRAEPITHELIAL CARCINOMA OF THE CERVIX, JAN. 1, 1947, THROUGH JUNE 30, 1954. 242 PATIENTS

						III				V		
	NO DIAG-		II			?		INTRAEP. ?	? INVASIVE	SQ. CELL CA. ?	SQ. CELL	
YEAR	NOSIS	I	II	IIA	II+	INTRAEP.	INTRAEP.	INVASION	MALIG.	INTRAEP.	CA.	TOTAL
1947				1	1				1	3	3	9
1948			2	1	3		1		7		2	16
1949	2		2		2	6	1	2	7		6	28
1950					5	13	12	9	4	5	2	50
1951			1	2	2	7	17	9	2	2	6	48
1952	1		1		1	5	9	6	3	4	9	39
1953				1	1	10	6	5	2	2	8	35
1954					2	2	3	2	2	3	3	17
Total	3	0	6	5	17	43	49	33	28	19	39	242
% of Total	1.2	0	2.5	2.1	7.0	17.8	20.2	13.6	11.6	7.9	16.1	

This classification was put into effect early in 1949. Thirty-eight intraepithelial lesions studied cytologically prior to that time were re-evaluated. The 242 noninvasive lesions discussed herein are distributed according to the revised classification as shown in Table II.

The atypical forms which we have found associated with intraepithelial carcinoma begin with Type II plus and progress in order of severity through Types III and V. Not to be included is the category under Type III for questionable invasive malignancy, in which are classified those smears which contain too few or poorly fixed cells, or malignant-appearing cells of indefinite character. Hence, there are six distinct categories used here for the classification of abnormal cells which represent intraepithelial carcinomas according to histologic diagnoses. These categories are based on cells, not always in the same combination, which

have a similar degree of abnormal morphology, *particularly of the nuclei.* The categories, therefore, are based not on cell patterns but on degrees of aberration from the normal.

It should be remembered that smears made from the same patient only hours apart may vary widely in their cellular components. This discrepancy can be due to several factors, including the important one of smear preparation. Although the cytologic classifications in the previous table are based on the first smears obtained from the patients, they do not represent necessarily the least or the most severe changes found in subsequent studies. Such a table, consequently, does not catalogue the atypicalities in all smears obtained from each patient.

We realize that noninvasive carcinoma must be defined by histologic studies. Nevertheless, in a certain number of patients, intraepithelial carcinoma can be recognized cytologically as a distinct probability; whereas, in a similar number of patients, noninvasive carcinoma is not distinguished from invasive. This point has been made by us in several papers, and also is emphasized here by Dr. Mackenzie.

Table II shows by means of our classification that in 144 patients, or 59.5 per cent of the total, the possibility of intraepithelial carcinoma was considered, and that in 49 patients, or 20.2 per cent of the total, the interpretation of a noninvasive lesion was not modified. It shows also that the cytology in 38 patients, or 16.1 per cent of the total, was thought to represent invasive carcinoma.

With regard to the cytologic identification of intraepithelial carcinoma in our work, *the malignant parabasal cell of Papanicolaou* continues to be the most reliable indication of the lesion. But, as we have said in an earlier paper, ''. . . there is not a single set of abnormal types of cells found in in situ carcinoma and another different set of abnormal types of cells found in invasive carcinoma. This conforms with histologic observations that a variety of differentiated and undifferentiated lesions are found in each category. Therefore, many different varieties of abnormal cells may be exfoliated from either, and some of the same varieties from both.''

Not all of the pathologic diagnoses were based on exhaustive studies of serial sections. The diagnosis in a large number was based on step serial sections. In this group, the patients who may have had invasive carcinoma are not known. An example is a patient who was listed in 1949 as having intraepithelial cervical carcinoma, and who was treated at that time by total hysterectomy. Metastases have occurred in the vaginal cuff and the vaginal wall, and at present there is an active lesion in an old simple vulvectomy scar. Recent examination of additional sections of the cervix demonstrated squamous-cell carcinoma. Another patient, aged 72, also was classified as having intraepithelial carcinoma and was treated by total hysterectomy. She died a year after operation with a frozen pelvis and distant metastases. Unfortunately, it is usually impossible to have sufficient personnel in the clinical pathology laboratory for the necessary adequate histologic study of this lesion.

TABLE III. AGES OF PATIENTS WITH INTRAEPITHELIAL CARCINOMA OF THE CERVIX

		AVERAGE AGES			
		INTRAEPITHELIAL CA. OF CERVIX (7 YEARS, 6 MONTHS)		SQUAMOUS-CELL CA. OF CERVIX (7 YEARS, 5 MONTHS)	
	AGE RANGE (YEARS)	YEARS	NO. OF PATIENTS	YEARS	NO. OF PATIENTS
White	23-71	41.0	175	48.8	440
Nonwhite	19-69	34.2	67	47.9	414
Combined	19-71	39.1	242	48.4	854

The ages of the 242 patients with intraepithelial carcinoma of the cervix (Table III) ranged, in white patients, from 23 to 71 years; in nonwhite patients, from 19 to 69 years. The average age for the 175 white patients was 41.0 years; for the 67 nonwhite patients (66 Negroes and 1 Croatan Indian), it was 34.2 years. Combined, the average was 39.1 years.

Not all of these patients had children, and not all were married. Forty-four, or 18.2 per cent, of these 242 patients were less than 30 years of age, and 88, or 55.4 per cent, were less than 35 years old (Table IV). It is significant that this is the youngest age at which women are admitted routinely to most cancer detection clinics. The occurrence of the tumor was most frequent in the fourth and fifth decades of life. One hundred sixty-three, or 67.4 per cent, of the 242 noninvasive carcinomas occurred in these years.

TABLE IV. AGE GROUPING OF INTRAEPITHELIAL CARCINOMA OF THE CERVIX, JAN. 1, 1947, THROUGH JUNE 30, 1954. 242 PATIENTS

AGE GROUP	WHITE	% OF WHITE	NONWHITE	% OF NONWHITE	TOTAL	% OF TOTAL	
15-19	0	0	1	1.5	1	0.4	
20-24	5	2.9	10	14.9	15	6.2	18.2
25-29	22	12.6	6	9.0	28	11.6	
30-34	21	12.0	23	34.3	44	18.2	
35-39	36	20.6	10	15.0	46	19.0	37.2
40-44	34	19.4	10	15.0	44	18.2	
45-49	25	14.3	4	6.0	29	12.0	30.2
50-54	9	5.1	1	1.5	10	4.1	
55-59	11	6.3	1	1.5	12	5.0	
60-64	4	2.3	0	0	4	1.7	14.5
65-69	7	4.0	1	1.5	8	3.3	
70-74	1	0.6	0	0	1	0.4	
Total	175		67		242		

We agree with Dr. Mackenzie in believing that intraepithelial carcinoma occurs in women of more than 50 years. Thirty-five, or 14.5 per cent, of these 242 patients are in this category.

At this point we should like to join Dr. Mackenzie in stressing again the need for adequate histopathologic study of the tissue obtained before a diagnosis of intraepithelial carcinoma is allowed to stand.

PREGNANCIES OBSERVED IN THE LIKELY-TO-ABORT PATIENT WITH OR WITHOUT HORMONE THERAPY BEFORE OR AFTER CONCEPTION*

CLYDE L. RANDALL, M.D., RICHARD W. BAETZ, M.D., DONALD W. HALL, M.D., AND PAUL K. BIRTCH, M.D., BUFFALO, N. Y.

(From the University of Buffalo and the Buffalo General Hospital)

HUMAN pregnancy fails to produce a healthy child so frequently that fetal loss remains a major problem. The desire to have a child becomes an obsession with some patients and, unfortunately, conception often proves difficult when the desire to have a child is most intense. To make matters worse, abortion is not unlikely when conception proves most difficult.

The size of the family often fails to reflect the couple's desire to have children, and little is done to help them so long as the physician regards abortion as the not undesirable loss of an imperfectly developing conceptus. As every progressive farmer knows, we should not be willing to blame the seed for a poor crop, so long as the soil can be improved. Although at this time we cannot improve the quality of the germ plasm involved, at least we now know effective methods of bringing the endometrium to an optimal "progestational" phase. Moreover, the means and ability to do so are widely available, and we can no longer justify a fatalistic attitude in regard to infertility or the recurrence of abortion and stillbirths.

Etiology of Abortion

There is no generally accepted agreement as to whether abortion usually occurs as the result of a transitory set of factors (the inadequacy of a particular corpus luteum or male fertility temporarily lowered by too frequent preovulatory intercourse, as Cross[6] describes), which would not necessarily persist and affect a particular couple's ability to accomplish a successful pregnancy with another try; or whether abortion, when it occurs, is usually due to factors which *can* be expected to persist and to affect each subsequent pregnancy until the pathology (congenital abnormality of the fundus, a "Lash" cervix,[17] or hypo-ovarianism with frequent anovulatory cycles and a poor endometrium) has been corrected by appropriate therapy.

Repeated or "habitual" abortion has been observed in 1.4 to 4.7 per cent of the pregnant women observed in several studies, whereas spontaneous abortion is usually believed to terminate from 10 to 20 per cent of all pregnancies. In a survey of 14,132 pregnancies among 5,000 women, however, Schoeneck[24] noted that 23.4 per cent of the patients accounted for 61.3 per cent of the abortions, premature labors, and malformations.

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

We believe there are at least two problems to be considered somewhat separately in the management of abortion. One patient may be threatening to abort as the result of a factor quite different from that which seems to predispose another woman to the recurrence of abortion. Measures must be therapeutic rather than prophylactic when abortion actually threatens and it is hardly reasonable to expect one and the same management to be equally effective in both situations. Being convinced that there are patients more "likely to abort," we suggest the following as situations in which abortion seems most likely to occur:

1. When in early pregnancy pathology or dysfunction is noted which is generally regarded as likely to increase the incidence of abortion. Included would be: (a) many situations that might complicate pregnancy, such as trauma, pathology requiring surgery (appendectomy, hemorrhoidectomy, occasionally splenectomy, etc.), emotional shock, etc.; (b) the discovery of congenital abnormalities of the uterus; or (c) detection by laboratory methods, of an endocrine dysfunction (poor progesterone level, for instance), that would jeopardize maintenance and development of the fetus.

2. When in early pregnancy, or before conception, the woman admits a "poor obstetrical history" such as: (a) difficulty in conceiving; (b) abortion of previous pregnancies; (c) fetal loss due to complications of late pregnancy probably due to faulty or inadequate placentation, such as prematurity or abruptio.

3. When in early pregnancy uterine bleeding is reported, and abortion seems threatened or imminent.

Prophylaxis When Abortion Seems Likely

The indications for treatment in the first situation described are certainly debatable. When something occurs which is physically or emotionally disturbing to the pregnant woman, or when a pathological condition is discovered which may jeopardize maternal health or the continued development of the pregnancy, yet no evidence of impending abortion is noted, is treatment indicated on a prophylactic basis? And, if so, what treatment?

We have recently reviewed[22] the records of 123 patients subjected to various types of surgery during pregnancy and found little evidence that the performance of indicated surgery during pregnancy will induce abortion or premature labor, even with no special management or treatment other than that indicated during convalescence from surgery. Physical stress, trauma, or emotional shock is not infrequently blamed for the occurrence of abortion, but every clinician of experience has watched pregnancies progress normally to term in spite of the most severe trauma or emotional strain. Studies adequate to assure recognition of abnormalities of the uterus indicate that some habitual aborters lose pregnancies because of uterine abnormalities which might be expected to affect the outcome of each subsequent pregnancy. Levine[18] has reported abnormalities in over 50 per cent of the uteri studied in a series of "habitual aborters." Recent reports of the findings when intrauterine exploration has been routinely carried out at the completion of the third stage of labor indicate, however, that congenital malformations of the uterus and submucous fibroids are not infrequently found after completion of a pregnancy carried successfully to term, in spite of uterine pathology which might have been expected to predispose the patient to abortion.

Ovarian hormones have long been employed in the treatment of threatened abortion, but in a purely empirical manner, with little concept of the deficiencies suspected or of the manner in which the hormones prescribed could be expected to be of benefit. Csapo,[7] quoting G. Anderson's estimate that 33 per cent of spontaneous abortions are due to functional uterine disorders ("FMD"), recently suggested a concept of the manner in which a progesterone deficiency might predispose to the "functional myometrial disorder" characteristic of the uterus which repeatedly aborts. Whether we visualize the infertile or aborting patient's difficulty as due primarily to an endocrine dyscrasia, or whether the patient's levels of hormones have been average, but inadequate for her particularly irritable uterus, it appears necessary to assure a quantity of hormone sufficient to maintain a progesterone-borne "defense mechanism against uterine contraction," which Csapo believes essential if the pregnancy is to be maintained. Thus it appears that when a factor apparently predisposing to abortion is recognized, if hormones are to be given, progesterone seems most logical. Additional amounts of progesterone would not, however, be advisable unless there is reason to suspect a deficiency.

Smears to Detect Progesterone Deficiency

In all probability considerable investigation was stimulated by the Smiths'[25] observations that the ingestion of stilbestrol during pregnancy would appreciably reduce the incidence of abortion (and certain late complications of pregnancy generally attributed to an inadequate placenta). While reading cervical smears in the Buffalo General Hospital in 1948, it occurred to Birtch and Hall that vaginal or cervical cytology might provide a means of recognizing the woman predisposed to abortion because of a progesterone deficiency. Anticipating that the relative amounts of progesterone effective in pelvic tissues might be evident in stained vaginal smears, it seemed possible thus to avoid some of the controversial loopholes of in vitro hormone assay. It has seemed likely that the progesterone effect evident in stained ectocervical epithelium must also be available and effective within the myometrium and decidua. Since October, 1949, smears have been taken (by one of the four of us working in one office) from the anterior portio vaginalis of somewhat over 3,000 women during the early weeks of pregnancy. Stained by the Papanicolaou technique, such smears have seemed to provide a practical and reliable measure of the relative adequacy or deficiency of progesterone effect.

We had hoped that this method of determining the progesterone level would provide a means of recognizing the patient "likely to abort." We have learned, however, that: (a) some patients abort with no evidence of progesterone deficiency (62 per cent of the women we observed before their abortion had no cytological evidence of progesterone deficiency, i.e., had a "good smear"); (b) sometimes a patient who shows a relatively poor smear will show spontaneous improvement in the smear and, without hormone treatment, her pregnancy will progress to normal completion at term. We would emphasize that while such a demonstrable deficiency as exists when increased cornification appears in the smear means that abortion is more likely to occur, nevertheless, 62 per cent of the spontaneous abortions in our series have occurred in spite of a good smear. Thus it appears evident that, at least in our experience, abortion frequently occurs when there has been no demonstrable deficiency of progesterone effect.

Effect of Stilbestrol on the Smear

Having demonstrated a prognostic value in the cytological method of estimating hormone assays, we were, of course, interested in seeing if we could

improve the progesterone effect (decrease the cornification evident in the smear), by the administration of stilbestrol to the patient who seemed predisposed to abortion because of a progesterone deficiency. We know that administration of stilbestrol to the nonpregnant woman would be expected to increase greatly the number of cornified cells in the smear.

Actually, we have noted that when smears have indicated a poor progesterone effect and no hormone treatment was given, 21.4 per cent of 117 patients aborted, whereas when smears indicated a poor progesterone effect and stilbestrol was given (in the dosage recommended by the Smiths) 19.3 per cent of 120 aborted in spite of the treatment. It has also been our impression that the ingestion of stilbestrol in recommended amounts did not reduce the incidence of abortion when good smears suggested no lack of progesterone effect.

Apparently the smears indicate an increased progesterone effect as a result of the ingestion of stilbestrol only when the prognosis for the pregnancy is good; i.e., when the early placenta *can* respond to the effects of ingested stilbestrol.

Since we have observed improvement in the smear (disappearance of cornified cells) occurring spontaneously—without the administration of hormone—we do not feel we can decide with certainty whether stilbestrol increased the progesterone effect or whether the improvement we have seen in the smear would have occurred without treatment.

It seems evident that *decreased cornification* (regarded as *increased progesterone effect*) will not be observed merely as a result of an increased level of stilbestrol in circulation. It now appears to us that, when those deficiencies in the early placenta and/or corpus luteum exist which account for a smear indicating a poor progesterone effect in a particular pregnancy, the giving of stilbestrol (in accordance with the dosage schedule recommended by the Smiths) does not increase the cytological evidence of progesterone effect in the tissues of a significant proportion of cases so treated. Moreover, we have not as yet observed evidence to suggest that the empirical and routine ingestion of stilbestrol, after conception occurs, appreciably reduces the over-all incidence of spontaneous abortion.

We have been most interested, however, in the fact that the cytological response to the ingestion of stilbestrol during early pregnancy seems to provide a therapeutic test of the early placenta's ability to function (or at least its ability to respond to a rising level of stilbestrol). If, when abortion threatens, and stilbestrol is given in accordance with the dosage schedule recommended by the Smiths, the number of cornified cells is few and tends to decrease further "on stilbestrol," the pregnancy will probably be maintained. If, however, the ingestion of such "adequate" amounts of stilbestrol is followed by noticeably increased cornification in the smears, then abortion appears inevitable. Actually, we believe that a missed abortion usually becomes evident when increased cornification appears after the ingestion of stilbestrol.

Management When Abortion Threatens

In a most helpful manner five years ago, Colvin's[5] report before this Association summarized the clinician's management of the woman threatening to abort. Emphasizing the importance and effectiveness of restricting activity, Colvin concluded at that time that the value of special diets, supplementary vitamin intake, and the prophylactic use of hormones had not been demonstrated.

We are all familiar with the controversial points concerning the etiology of abortion, particularly in regard to attempts to establish the frequency of malformation or absence of the fetus in the early conceptus. In this country, Mall[19] and more recently Hertig and Rock[10] are largely responsible for the frequently expressed opinion that nearly half of the spontaneous abortions occur because of some defect of the embryo. Such developmental defects have been generally regarded as an indication of abnormality or deficiency of ovum or sperm, and J. Botella-Llusia[3] very recently reported that "an abnormality of the ovum" was found in 4.7 per cent of all pregnancies observed and in 47.3 per cent of the spontaneous abortions studied.

We believe it is important to consider the probability that many of the embryonic defects previously attributed to faulty germ plasma may have been due to inadequate nutrition of the conceptus in the earliest stages of its development. This possibility makes it difficult to evaluate reports regarding the incidence of blighted ova and malformations when the products of abortion have been examined histologically. It is equally difficult to make certain that the levels of pregnandiol in the urine parallel suspected variations in the concentration of progesterone effective in the uterus of early pregnancy. Certainly the latter determination appears to be a most significant finding when abortion threatens.

If a lack of progesterone is a chief factor in the etiology of abortion, then the rapid administration of progesterone appears to be the most logical treatment when abortion threatens. Karim and Wahba[15] have recently reported a series of 50 women, threatening to abort, who were treated by intravenous administration of progesterone. Since it has been our experience that approximately four times as many patients report bleeding in pregnancy as actually abort, we have been interested in the apparent effectiveness of their use of progesterone. Twenty-four per cent of our patients reported bleeding in early pregnancy and were regarded as threatening to abort but only 6.6 per cent (27.5 per cent of those who bled) actually aborted. As shown in Table I, Colvin also reported that 28 per cent of the patients who bled in early pregnancy actually aborted. We believe it is interesting in Table I that only 38 per cent of our patients who aborted had previously shown a poor smear (indicating a deficiency of progesterone). Karim and Wahba treated all women who threatened to abort with intravenous progesterone and reduced the proportion who actually aborted to 18 per cent. We might suspect that the difference between their 18 per cent and Colvin's 28 per cent represents the 38 per cent of aborting women who we found had a "poor smear" (and needed progesterone!) (38 per cent of 28 = 10.6).

TABLE I. SUMMARY OF OBSERVATIONS REGARDING ABORTION

When Abortion Actually Threatens.—		
Colvin (1949):	28% of those threatening actually aborted.	
Present report:	24% of patients reported bleeding.	
	6.6% actually aborted.	
	Hence 27.5% of those threatening actually aborted.	
Etiological Factors.—		
Hertig and Rock (1949):	Abnormalities of conceptus	43%
G. Anderson (Csapo, 1954):	Functional myometrial disorder	33%
Present report:	Deficiency of progesterone ("poor smears")	38%
Treatment.—		
Colvin (1949):	Bed rest (1,570 cases)	28% aborted
Karim and Wahba (1954):	Intravenous progesterone (50 cases)	18% aborted

Treatment of Habitual Abortion

In recent years emphasis has been placed upon the obstetrical history when abortion threatens. The woman with a history of infertility or previous abortion seems more likely to abort spontaneously than is the woman who has conceived without difficulty and has carried previous pregnancies to term. Although Colvin's group were not impressed by evidence in their material that a woman who had previously aborted would be inclined to lose the next pregnancy, Schoeneck, Hughes, and associates[24] have since emphasized the apparent relationship between infertility, abortion, and the complications of late pregnancy referable to an inadequate placenta. The importance of the obstetrical history has also been noted by Levine and associates.[18]

Figures from our own practice affirm the prognostic value of a poor obstetrical history. Reviewing the records of women who have had three or more pregnancies, we first divided them into two groups: (1) those with a "good obstetrical history" were the women who had failed (by abortion or a stillbirth due to placental inadequacy—previa, abruptio, or premature labor) but once in three pregnancies to deliver a live child at term; (2) those with a "poor obstetrical history" were those who lost two-thirds or more of their pregnancies because of some placental inadequacy. When all other factors were disregarded, and the outcome of the present pregnancy was compared among women with a good obstetrical history and those with a poor obstetrical history, abortion was found to have occurred twenty times more frequently when the previous obstetrical history was "poor."

It is evident that we cannot modify or improve the obstetrical history of women who seek aid after the loss of several pregnancies. Much available evidence suggests, however, that we need not wait until the patient has experienced three consecutive abortions, and has thus fulfilled the criteria of a habitual aborter, to recognize her problem as a serious one. Obviously there is need to institute measures to improve the probability of her carrying the next pregnancy to term before the disheartening loss of a third conception. We would do well to remember, for instance, that some spontaneous abortions have been reported[4] due to such transitory pathology as may be eradicated by simple curettage when a first abortion occurs.

In a 1953 summary of the reported histories of 1,820 habitual aborters whose management had been reported by 14 authors, King[16] concluded that, whatever treatment was employed, a successful outcome was reported in 61 ± 1.14 per cent of the cases (Table II).

TABLE II. PROPHYLACTIC HORMONE THERAPY FOR THE LIKELY-TO-ABORT PATIENT

AUTHOR	TREATMENT	PER CENT SUCCESSFUL PREGNANCIES
King (1953)		
Summary 1,820 cases	"Whatever treatment used"	61± 1.14
Smith and Smith (1954)		
81 cases	Stilbestrol	74.0
Kamal (1954)		
44 cases	Progesterone (implants)	66.6
	Progesterone (microcrystals)	82.7
Javert (1954)		
100 cases	"Current therapy"	92.5
Hughes		
90 cases	"Preconceptional" treatment	90.0
Present Report		
49 cases	9 per Smith and Smith	66.6
	10 per Hughes	60.0
	30 with inadequate treatment	63.3

While the importance of evaluating the male is never questioned when apparent sterility is the problem, there is little evidence that even repeated abortion is due to deficiencies on the part of the male. Joel[13] has recently reported a few convincing case histories, but such instances probably do not account for an appreciable proportion of the fetal loss that is due to abortion.

At the International Congress a few weeks ago, both Warkany[28] and Halbrecht[9] reported that dietary deficiencies are not likely to account for the incidence of abortion or premature labor. While Javert[12] has repeatedly emphasized that an intake of vitamins C and K in excess of that provided by the average American diet will increase the number of successful pregnancies among a series of "habitual aborters," his most recent publications lists 14 specific measures included in the regimen described as "current therapy," which he credits for the successful outcome of 25 (92.5 per cent) of 27 pregnancies which occurred in 24 habitual aborters so managed. Javert's discussion implies that any effort to judge the effectiveness of any one of the factors considered is likely to be misleading unless all other measures are maintained as constants during the period the one factor is omitted from the "routine." Perhaps few of us have the opportunity or the ability to maintain an appreciable number of patients on a regimen comparable to that outlined by Javert's fourteen points, but, having failed to do so, it seems evident that we should be slow to credit a less comprehensive program with the results we have observed.

We are all familiar with the studies and controversy following the Smiths' reported results with the use of stilbestrol. We believe that Dieckmann and Davis[8] have shown conclusively that the routine administration of the Smiths' recommended dosage of stilbestrol to all pregnant women does not appreciably reduce the rate of occurrence of spontaneous abortion or those complications of late pregnancy generally attributed to inadequacy of the placenta. And in our own data[23] we could find little evidence that the routine administration of stilbestrol lowers the incidence of abortion even when the patient's smear indicated a progesterone deficiency in that particular pregnancy. If, on the other hand, the administration of stilbestrol is restricted to those individuals with a bad obstetrical history, Plate[21] reports data and quotes others supporting the Smiths' contention that stilbestrol treatment, given only to women with a poor obstetrical history, greatly increases their percentage of successful pregnancies. As shown in Table II, the Smiths[25] recently reported that 74 per cent of their 81 habitual aborters treated by oral stilbestrol have carried to term. When smears indicate there is a relative deficiency of progesterone in early pregnancy, we have not been able to show evidence that the giving of stilbestrol improves the progesterone effect in the vaginal and cervical tissues of a significant proportion of cases so treated. It is evident, however, that certain other effects of stilbestrol, such as an increased vascularity of the uterus, may account for a better salvage rate when stilbestrol is given to the habitual aborters before abortion threatens and in accordance with the Smiths' recommendations regarding dosage.

If a lack of progesterone effect is a chief factor in the etiology of repeated abortion, we would expect to find, paricularly when conception occurs in the poor-obsterical-risk patient, that the prompt and continued administration of adequate amounts of progesterone would materially reduce the incidence of abortion. This was suggested at the recent Geneva Congress, when Kamal[14] reported the data shown in Table II. Since Swyer[27] and Bishop[2] had also treated 27 and 32 such patients with implantations of progesterone in pellet form with success in 74 per cent and 72 per cent of pregnancies, respectively, the uniformity of good results seems truly remarkable. It is well

to remember, however, as Colvin had previously reported and Bevis[1] has emphasized, that bed rest alone seems appreciably to improve the percentage of pregnancies carried to term by even the habitual aborter, and certainly avoidance of apprehension and stress is emphasized in Javert's "current therapy."

Remembering that Malpas[20] has estimated that a successful outcome of another pregnancy could be anticipated in only 27 per cent of cases with a history of three or more previous abortions, all forms of treatment appear better than no treatment. We are inclined to believe, however, that the most logical and effective management of the habitual aborter yet proposed was that outlined by Hughes[11] before this Association five years ago. It has seemed logical to evaluate carefully the patient's ability to approach her time of ovulation with an endometrium adequately prepared for nidation (nutritionally as well as histologically) and to avoid conception until such time as preconceptional studies indicate an adequate endometrium.

The importance of preconceptional management was indicated by Sullivan's[26] study of the optimal interval between pregnancies after spontaneous abortion had occurred. Sullivan's group observed that 75 per cent of women ovulate within three to four weeks following a spontaneous abortion, but they recommend that after completion of a spontaneous abortion, conception be avoided until three "normal periods" have occurred at fairly regular intervals, an observation adding to the evidence that preconceptional assurance of endometrial "readiness" is of the utmost importance.

Two observations in our own experience seem to indicate the effectiveness of preconceptional treatment. We have been impressed with the frequency with which women whose dysfunctional bleeding was being managed by the cyclical administration of estrogen plus premenstrual progesterone became pregnant and progressed normally through an uneventful pregnancy. Even more impressive have been a number of women who, after evaluation and treatment of infertility, climaxed by several months on the preconceptional regime advocated by Hughes, accomplished a pregnancy which progressed normally to term. To date, we have been impressed by the relative infrequency of abortion when conception has been accomplished after preconceptional study indicates endometrial readiness.

Observations

A. When cytology in early pregnancy indicates *adequate* progesterone effect (2,541 pregnancies):

92.6% pregnancies terminated in birth of live child,
5.0% pregnancies terminated in abortion (no treatment).

When a gravida iii plus with a *poor obstetrical history* has a *good smear* in her present pregnancy (258 patients):

92.1% pregnancies terminated in birth of live child.

When a gravida iii plus with a *poor obstetrical history* has a *good smear* in her present pregnancy (41 patients):

85% pregnancies terminated in birth of live child.

B. When cytology in early pregnancy indicates *a relative deficiency of progesterone* (311 patients):

48.7% pregnancies terminated in birth of live child,
24.1% pregnancies terminated in abortion.

When a gravida iii plus with a *good obstetrical history* has a *poor smear* in her present pregnancy (33 patients):

72.7% pregnancies terminated in birth of live child.

When a gravida iii plus with a *poor obstetrical history* has a *poor smear* in her present pregnancy (10 patients):

no live babies, 49 pregnancies without birth of a single live child.

C. When the bad obstetrical risk is managed according to the Smiths' regime of postconceptional stilbestrol therapy:

74% pregnancies terminated in birth of a live child (81 cases, Smith and Smith[22c]).

D. When the bad obstetrical risk is managed according to Hughes' recommendations regarding preconceptional treatment:

90% pregnancies terminated in birth of a live child (90 cases, Hughes [personal communication]).

E. We have managed 49 habitual aborters:

9 given stilbestrol per the Smiths' regime,
6 delivered live babies.
10 became pregnant on Hughes' preconceptional treatment,
6 delivered live babies.
30 were not adequately prepared per Hughes' criteria before conception and were given no hormones after conception.
19 delivered live babies.

Treated cases 19, live babies in 63.2 per cent.
Not adequately treated 30, live babies in 63.3 per cent.

Comment

As we contemplate the unhappiness of infertility, it is well to remember that happiness itself, at least according to some philosophers, cannot be assured by its mere pursuit. Certainly the mere persistence of effort and the occasional occurrence of conception (which is likely to abort) is neither assurance nor reward for the couple anxious to have a child.

A review of the current literature regarding the etiology and prevention of abortion usually leaves one unconvinced of the value of many of the specific measures that have been recommended.

We are still inclined to agree with Colvin's 1950 statement that once abortion threatens, bed rest is the most important measure. We would now add, however, particularly if there is evidence of a progesterone deficiency, that the prompt and rapid administration of progesterone may decrease the incidence of abortion from 28 to 18 per cent. For the management of the habitual aborter, we believe Hughes has shown that an effective time for treatment designed to decrease the incidence of abortion would be before conception occurs rather than at the time abortion threatens.

We must not expect to find a cure-all, for it is becoming more and more evident that much wastage will continue so long as our therapy consists of the routine employment of some particular measure, to the exclusion or neglect of other factors which may be equally important. In all probability we should not attempt to estimate the effectiveness of specific or single factors, except by their omission or addition to the comprehensive type of regime described by Javert as "current therapy."

Summary

Bleeding suggesting threatened abortion may be expected in 20 to 25 per cent of pregnancies.

When abortion threatens:

A. Approximately 28 per cent will abort if treatment consists only of bed rest.[5]

B. The routine administration of stilbestrol to all pregnant patients does not reduce the incidence of abortion or fetal loss.[8]

A cytologically demonstrable deficiency of progesterone was noted in 38 per cent (approximately one-third) of the patients who later aborted their pregnancies.

A. The 11 per cent of patients with evidence of a progesterone deficiency accounted for 36.6 per cent (approximately one-third) of the spontaneous abortions we have observed.

B. The routine administration of stilbestrol to all patients who show cytological evidence of a progesterone deficiency in early pregnancy does not seem to decrease significantly the incidence of spontaneous abortion even among such patients (21.4 to 19.3 per cent[23]).

C. Prompt administration of progesterone (intravenously) to all patients who threaten to abort reduces the proportion actually aborting from 28 to 18 per cent[15] (the one-third who show progesterone deficiency?).

In the management of the patient likely to abort because of a bad obstetrical history:

A. We have observed no fetal survival when a patient with a bad history also had a cytologically evident deficiency of progesterone early in the pregnancy.

B. The postconceptional administration of stilbestrol might be credited for some fetal survivals but such live births were observed only when there had been no cytological evidence of progesterone deficiency early in the pregnancy.

C. The placental adequacy characteristic of the pregnancy associated with a good smear and a relatively lower incidence of fetal loss seems most likely to be assured by preconceptional "priming"[11] of the endometrium.

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Discussion

DR. DONALD G. TOLLEFSON, Los Angeles, California.—The classification into two groups of cases, one with a good obstetric history and the second with a poor obstetric history, combined with the cytologic studies, seems to be a logical approach to the prognosis.

We have continued to use stilbestrol, according to the routine recommended by the Smiths, as a prophylactic measure and also in the threatened abortions, but we have been disappointed with our results. We have also used progesterone in threatened abortions. While we have not had any experience with the cytologic method of demonstrating progesterone activity, it apparently has considerable merit. We continue to use thyroid when it is indicated by the blood iodine and basal metabolic rate, but also empirically, and believe that it is definitely of value. It is difficult to evaluate one modality of treatment; we must consider all factors. From a practical standpoint we must make use of all those methods which may save pregnancies.

We have been interested in Dr. Hughes' preconceptional treatment of the endometrium, and we believe that it should be one of our first considerations in treating these likely-to-abort patients. How frequently we are asked by our patients, "What can be done before I conceive so that this accident will not happen again?" In the past we have required a general physical examination, including a blood count, urinalysis, and basal metabolism test. We have made use of adequate diet, vitamins, and rest; but here is something additional we can propose which seems more logical to us and will be readily accepted by our patients. It may be that a more careful review of the obstetric history will influence the use of preconceptional therapy.

Dr. Randall reports abortions in only 6.6 per cent of the 24 per cent of his patients who bled early in pregnancy. This is a most enviable record, and indicates that whatever management was used was most successful.

The fact that 62 per cent had a good smear showing no evidence of progesterone deficiency before abortion occurred and that only 38 per cent who aborted had poor smears indicates that this deficiency is only one of the factors to be considered. This fact is emphasized by the author.

Again it must be repeated that the problem has many facets, and it is difficult to evaluate any one of them without considering the others.

DR. E. D. COLVIN, Atlanta, Ga.—The use of any diagnostic procedure or the results obtained by any form of therapy which allegedly influences the outcome of pregnancy among women in whom abortion has previously occurred, or is threatened, must be evaluated in the light of information obtained by a careful study of products expelled when the process is permitted to terminate naturally among untreated women. Operative interference fails to permit a study of the product. Consecutive private patients seem to constitute the ideal background for such a study. In such a group, the incidence of criminal abortion would be negligible and the possibility of obtaining satisfactory specimens would appear most likely.

In our practice, with the exception of an occasional case of missed abortion, we have refrained from operative interference in the termination of abortions. As has been previously reported, we have found that past obstetric performance is without value in the prognosis of pregnancy among women considered as likely to abort. Bevis (Lancet 2: 207, 1951) and Speert (AM. J. OBST. & GYNEC. 68: 665, 1954) have expressed the same opinion. Dr. Randall's observation that 62 per cent of the abortions in his series occurred in spite of satisfactory cytologic smears seems to reflect doubt on the prognostic value of this procedure.

We have been impressed with the frequency with which the great majority of aborted products are associated with evidence of defective embryonic or fetal development, especially blighted ova. This finding among patients attended by the Bartholomew Group causes us to continue to doubt the value of prophylactic therapy in the prevention of abortion. Therefore we have refrained from its use.

In a recent unpublished study, although 24.2 per cent of our patients were found to have experienced bleeding during the early weeks of pregnancy, we found that the abortion rate among our patients was only 5.5 per cent—a figure considerably less than those usually quoted in the literature. We found further that 82.2 per cent of the abortions were due to blighted ova and defects in fetal development.

Of 52 untreated women who had experienced three or more consecutive abortions before, between, or following term pregnancies in a total of 262 conceptions, all but 6, by persistence of effort alone, achieved one or more living infants—a success rate of 85.5 per cent. In this group 209, or 79.6 per cent of the total pregnancy losses, were due to developmental failures in embryonic growth.

In another group of 162 women who, under similar circumstances, had experienced two consecutive abortions in a total of 596 pregnancies, all but 12, or 7.4 per cent, by persistence of effort alone achieved one or more living infants. In this group, 495, or 83.1 per cent of the losses, were due to defective embryonic development. These results obtained by persistence of effort alone seem to indicate a lack of recurrent causative factors in the majority of abortions among our patients.

The demonstration by Hertig and his co-workers that a pathologic embryo is the most common single factor in spontaneous abortion, and their later discovery of embryonic abnormalities in 42 per cent of very early conceptuses appears to indicate that the aim of the therapist should be in the direction of improving the formative cells of the ovum rather than its implantation bed. In this connection, the observations of Thiersch (AM. J. OBST. & GYNEC. 63: 1298, 1952) demonstrating the destructive effect of a folic acid antagonist on early embryonic growth, indirectly suggest a new therapeutic approach to fetal salvage possibilities among women considered as likely to abort. The possible value of prophylactic folic acid therapy can, at present, however, be only speculative.

Undoubtedly progesterone plays an important part in the preparation and preservation of the implantation bed during pregnancy. It is accepted, as has been shown by Dr. Randall and his associates, that cytologic studies give evidence of progesterone activity; however, cytologic findings fail as a criterion of the developmental status of the embryo.

Although several methods for determining viability of the embryo in the presence of threatened abortion have been described, an entirely satisfactory one is yet unknown. In our experience, a fairly high percentage of accuracy is thought possible by a careful consideration of the knowledge gained from an evaluation of signs and uterine changes over a period of time.

The time of the initial bleeding apparently is of prognostic value. When it appeared as a single episode at or near the time of the first missed menstrual flow—usually as a pink smear or slight gush of bright red blood—it was found that abortions occurred in only 5 per cent of the cases (Table I). Of these abortions, 40 per cent were due to blighted ova. On the other hand, if the initial bleeding occurred about the time of the first missed menstrual flow and continued over a period of several days or weeks, or if it developed later, as was true in the majority of the cases, abortion occurred in 28 per cent. Of the abortions in this group, 84 per cent were due to blighted ova.

TABLE I. RELATIONSHIP OF TIME OF ONSET OF INITIAL VAGINAL BLEEDING AND OUTCOME OF PREGNANCY

	BLEEDING ONLY AT OR NEAR TIME OF FIRST MISSED FLOW 205 CASES (22.9%)	BLEEDING CONTINUED FROM FIRST MISSED FLOW OR DEVELOPING LATER 689 CASES (77.1%)
Term or premature labor	195 (95%)	496 (72%)
Abortion, all causes	10 (5%)	193 (28%)
Blighted ovum	4 (40%)	163 (84%)

The color of the discharge seems to be of great prognostic value. Initial brown discharge, continuing as such, or becoming brownish red in color, seems to portend abortion due to blighted ova, as was found in 71 per cent. When the initial bleeding was bright red, usually occurring as a single episode, often in considerable amount and tapering off to brown in color, it was found that only 10 per cent aborted.

Deficiency in the size of the uterus is readily recognized, and furnishes confirmatory evidence of a blighted ovum in the presence of uterine bleeding.

DR. J. ROBERT WILLSON, Philadelphia, Pa.—I should like to bring to your attention a study which is being carried on by Dr. Forman, who is in charge of our infertility clinic, a preliminary report of which was given at the recent meeting in San Francisco.

As you know, the cervical mucus, when it is smeared on a glass slide, dried, and examined microscopically, will show a crystallization phenomenon called "ferning" if the estrogen levels are high enough. The higher the estrogen level, the more complete the ferning phenomenon; but the fern phenomenon can be prevented, even with very high estrogen levels, by the administration of enough progesterone. During pregnancy the fern phenomenon normally is absent, and it is impossible to induce ferning, even if exceedingly high doses of estrogen are administered exogenously.

Dr. Forman has reported upon a series of patients with a positive fern phenomenon in early pregnancy, and at this point it appears that his findings are confirmatory of those of Dr. Randall and his associates, so ably presented in this excellent study. If there is positive ferning in the cervical mucus in early pregnancy, the majority of the pregnancies terminate either in abortion or in some placental accident. It appears to us that the positive fern phenomenon in these pregnanies is due to a deficiency of progesterone which will not permit the pregnancy to maintain itself normally. I believe that this conclusion is similar to those drawn by Dr. Randall and his associates.

DR. PAUL K. BIRTCH.—The initial assumption on which this work was based is that the epithelium of the woman's generative tract mirrors the function of the ovary or any sex steroids, regardless of their origin. Therefore, we thought that perhaps the cytologic method might be a means of determining when a threatened abortion is on the basis of a sex-steroid deficiency.

We take the smear by the use of a speculum, prior to digital examination. The smear is secured from the anterior fornix of the vagina, because we believe it is the cleanest area of the vagina. If there is much discharge present even in that location, we first wipe it away and then take the smear.

Dr. Traut has shown that during pregnancy it is the mid-zone of the vaginal epithelium that undergoes tremendous hypertrophy, and that all cells seen on cytologic spread during pregnancy are probably derived from this zone. There should be no cornification in the smears of pregnant women who are progressing normally, and all the cells should be basophilic transitional-layer cells. When the number of cornified cells approximates 35 per cent, we believe that this represents a moderate increase in cornification, and that one of two things will happen, either the patient will abort or her smears will revert to normal, with or without therapy. If she is going to abort, the process goes further, and her smears become the full-blown cornification type.

We have had this experience in cases of threatened abortion where the smears showed a moderate increase in cornification: After the patient was given stilbestrol according to the Smith and Smith regimen, her symptoms of abortion would disappear and she would think everything was well. Then when the smear was repeated two weeks later it would show full-blown cornification, indicating a missed abortion. That is an interesting sidelight to this work—that we have created many missed abortions, I believe, by the use of stilbestrol.

The total number of patients in our series whose smears indicated a poor progesterone effect when stilbestrol was given was 113. Of these, 19.3 per cent aborted. In a similar series with a good smear, who were given stilbestrol according to the Smith and Smith regimen, only 4.7 per cent aborted. In patients with the "moderately increased cornification" type of smear, the incidence of abortion is almost 4½ times as great, or 20 per cent. Of those patients whose smears showed a poor progesterone effect and who were not treated, 21 per cent aborted.

All these data seem to suggest that the presence of a deficiency great enough to be demonstrable in the smear as increased cornification means that abortion is more likely to occur. Nevertheless 76, or 62 per cent, of the spontaneous abortions occurred in spite of a good smear. Obviously, then, abortion occurs in many instances when there is no demonstrable sex-steroid deficiency, and it has been our experience that the ingestion of stilbestrol in recommended amounts does not reduce the incidence of abortion when smears suggest no hormonal deficiency.

DR. RANDALL (Closing).—I would like to correct one impression I think Dr. Tollefson has that I hope many of you do not have. I did not mean to give the impression that only 6.6 per cent of the patients who threatened to abort actually aborted. We do wish to report that 24 per cent of all our patients threatened to abort, and that 6.6 per cent of all patients actually aborted. This means that 27.5 per cent of our patients who threatened to abort actually aborted, and agrees very closely with Dr. Colvin's 1950 figure of 28 per cent.

I have no comment about Dr. Colvin's observation today that 82 per cent of their patients who abort show evidence of a blighted ovum. That seems pretty high—discouragingly high to someone who is trying to treat these situations on the basis of a suspected hormone deficiency. We do feel, on the basis of our own observations, that approximately 60 per cent of abortions are not based on progesterone deficiency. I hope, however, that Dr. Colvin will be generous enough to let us feel that we might be able to do something for at least a third of these patients.

I believe our problem at the present time is to recognize the patient that we can do something for, and then to give her whatever hormone is lacking. It looks to us as if that usually is progesterone.

CONCEPTION-EFFORT TIME IN RELATIONSHIP TO FETAL WASTAGE*

Preliminary Report

F. J. SCHOENECK, M.D., SYRACUSE, N. Y.

(From the Bureau of Maternal Hygiene, Department of Health, Syracuse)

RECENT studies[1] in Syracuse concerning fetal and infant loss have suggested that the major solution of the problem depends on correction of its obstetrical aspects.

Many approaches are involved. One of them, which apparently has definite possibilities, is the preconceptional study and treatment principle for handling cases which have shown poor pregnancy patterns. Hughes and his group[2] are presently using this method in handling patients with histories of recurrent premature labor, previous congenitally defective offspring, and chronic abortion.

I[3] have previously reported that, in addition to the women with specific patterns of pregnancy wastage previously enumerated, others also show a disproportionate pregnancy wastage. Prevention of bad outcomes of pregnancy in this relatively small number of women could, theoretically, be a major step in solving the problems of pregnancy wastage.

It appears that identifying these women before they develop their "bad patterns" of pregnancy and treating them preconceptionally would be a logical approach to solving the problem.

This preliminary report deals with the aspects of attempting to identify those women who will have disproportionate pregnancy wastage early in the childbearing period, so that they may be studied and treated prophylactically.

We have theorized that correlation of menstrual history, conception-effort time, and the outcome of the first or first and second pregnancies might give clues by which these women could be identified.

The ensuing report deals only with the information we have accumulated on conception-effort time.

Data on 8,032 pregnancies (of which 166 were twins and one a set of triplets) studied in Syracuse from April 1, 1953, to April 1, 1954, provide the material for this preliminary report.

Technique of the study consists of interviews, by public health nurses, of patients hospitalized with any pregnancy diagnosis in all Syracuse hospitals. Interviews with private and clinic patients were made during the patients' hospitalization. Approximately 90 per cent of such patients admitted were interviewed. Among other things, specific data on the length of time it took the patient to become pregnant were ascertained.

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*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

Conception-effort time was classified as follows:

Class A: Conception-time effort 1 to 3 months
Class B: Conception-time effort 3 plus months to 12 months
Class C: Conception-time effort 1 year to 5 years
Class D: Conception-time effort More than 5 years
Class E: "Accidental" (usually failure of some contraceptive method)
Class F: Patients could not give specific data desired

Table I shows the conception-effort time in 5,556 pregnancies in which patients were able to give positive information on the length of time it took them to conceive.

3,338 (60.07%) fell in Class A
1,326 (23.86%) fell in Class B
715 (12.86%) fell in Class C
177 (3.18%) fell in Class D

Table I further illustrates the percentage of these patients who had examinations and/or treatment because of inability to conceive. "Sterility" in Classes A and B obviously does not meet the usually accepted standards for placing a patient in such a category (i.e., one year's unsuccessful conception effort). The figures are included since the patients did receive such attention.

TABLE I. CONCEPTION-EFFORT TIME (POSITIVE INFORMATION), 5,556 PREGNANCIES

	NO.	%	STERILITY RATE (%)
Class A 1-3 months	3,338	60.07	.71
Class B 3 months-1 year	1,326	23.86	6.86
Class C 1-5 years	715	12.86	18.46
Class D 5 plus years	177	3.18	20.90

It will be noted that approximately 20 per cent of the patients who had real sterility problems (i.e., unsuccessful conception-effort time of more than a year) received medical attention for this condition.

The accurate outcome of the pregnancies in all cases was recorded, from hospital records, according to the following classification:

Full term (5 pounds, 8½ ounces or larger) — Living
Large premature (3 pounds, 5 ounces to 5 pounds, 8 ounces) — Neonatal death
Small premature (1 pound, 1½ ounces, approximately, to 3 pounds, 4½ ounces) — Infant death / Stillborn
Abortion, proved (fetus* observed or microscopic identification of products of conception)
Abortion, probable (gross observation of tissue by physician)
Abortion, possible ("tissue" observed by patient)
Ectopic pregnancy—abdominal pregnancy—hydatidiform mole
Major and minor congenital defects were also recorded.

Data were likewise obtained on nonhospitalized deliveries and abortions, by voluntary reporting on special forms, from physicians in the Syracuse area. These patients were not interviewed by public health nurses, but when available, the physicians supplied the conception-effort information.

The outcome of pregnancy in relation to the conception-effort time is recorded in Tables II to VI.

Table II shows the number and percentage of term babies (living, neonatal deaths, infant deaths,† and stillbirths) for each conception-effort time

*For purposes of this study, any fetus weighing less than 500 grams (approximately 1 pound, 1½ ounces) is classified as an abortus.

†Corrected to May 1, 1954.

class. It will be noted that the percentage of neonatal deaths and stillbirths in Class D conception-effort time may be of significance.

Table III presents similar data for the group of larger prematures (3 pounds, 5 ounces to 5 pounds, 8 ounces). The percentage of necnatal deaths and stillbirths in Class D may, as in the "term" group, be of significance.

Table IV gives those data for the group of smaller prematures (1 pound, 1½ ounces, approximately, to 3 pounds, 4½ ounces).

Table V includes the conception-effort time for the various types of abortion (proved, probable, and possible). It will be noted that there is an apparent increase in incidence of proved abortions as the length of conception-effort time increases.

Table VI outlines the findings for ectopic pregnancy, abdominal pregnancy, and hydatidiform mole. Attention is called to the percentage of ectopic pregnancies which are included in Class D conception-effort time.

Table VII shows the incidence of major and minor congenital defects, both fatal and nonfatal, according to the various conception-effort time classes. The findings with the Class D patients, again, may be of significance.

TABLE II. TERM INFANTS (5 POUNDS, 8½ OUNCES, PLUS) IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME			OUTCOME OF PREGNANCY							
			LIVING		NEONATAL DEATHS		INFANT DEATHS		STILLBIRTHS	
			NO.	%	NO.	%	NO.	%	NO.	%
Class A	1-3 months	(3,338)	2,993	89.66	14	0.41	9	0.26	20	0.59
Class B	3 months-1 year	(1,326)	1,174	88.53	9	0.67	2	0.15	4	0.30
Class C	1-5 years	(715)	633	88.53	1	0.13	2	0.27	2	0.27
Class D	5 plus years	(177)	140	79.09	2	1.12	1	0.56	2	1.12
Class E	"Accidental"	(1,506)	1,263	83.36	10	0.66	5	0.33	13	0.86
Class F	Not known	(970)	781	80.51	10	1.03	8	0.82	13	1.34

TABLE III. LARGE PREMATURES (3 POUNDS, 5 OUNCES TO 5 POUNDS, 8 OUNCES) IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME			OUTCOME OF PREGNANCY							
			LIVING		NEONATAL DEATHS		INFANT DEATHS		STILLBIRTHS	
			NO.	%	NO.	%	NO.	%	NO.	%
Class A	1-3 months	(3,338)	135	2.96	12	0.26			4	0.11
Class B	3 months-1 year	(1,326)	57	4.29	1	0.07			3	0.67
Class C	1-5 years	(715)	31	4.33	2	0.27	1	0.13	2	0.41
Class D	5 plus years	(177)	11	6.21	2	1.12			2	1.12
Class E	"Accidental"	(1,506)	78	5.17	5	0.33	1	0.06	3	0.19
Class F	Not known	(970)	36	3.17	11	1.13			8	0.61

TABLE IV. SMALL PREMATURES (1 POUND, 1½ OUNCES TO 3 POUNDS, 4½ OUNCES) IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME			OUTCOME OF PREGNANCY							
			LIVING		NEONATAL DEATHS		INFANT DEATHS		STILLBIRTHS	
			NO.	%	NO.	%	NO.	%	NO.	%
Class A	1-3 months	(3,338)	6	0.11	29	0.68			19	0.56
Class B	3 months-1 year	(1,326)	9	0.67	6	0.45			6	0.45
Class C	1-5 years	(715)	3	0.41	5	0.69			6	0.83
Class D	5 plus years	(177)	2	1.12	2	1.12				
Class E	"Accidental"	(1,506)	3	0.19	11	0.73			12	0.79
Class F	Not known	(970)	6	0.61	15	1.54	2	0.26	14	1.44

TABLE V. ABORTION IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME	OUTCOME OF PREGNANCY					
	PROVED ABORTION		PROBABLE ABORTION		POSSIBLE ABORTION	
	NO.	%	NO.	%	NO.	%
Class A 1-3 months (3,338)	69	1.88	17	0.47	7	0.17
Class B 3 months-1 year (1,326)	34	2.56	9	0.67	1	0.07
Class C 1-5 years (715)	21	2.93	1	0.13	2	0.27
Class D 5 plus years (177)	7	3.95	1	0.56	2	1.12
Class E "Accidental" (1,506)	73	4.84	7	0.46	7	0.46
Class F Not known (970)	46	4.74	12	1.23	5	0.57

TABLE VI. OUTCOME OF PREGNANCY, VARIOUS, IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME	OUTCOME OF PREGNANCY					
	ECTOPIC PREGNANCY		ABDOMINAL PREGNANCY		HYDATIDIFORM MOLE	
	NO.	%	NO.	%	NO.	%
Class A 1-3 months (3,338)	4	0.11				
Class B 3 months-1 year (1,326)	1	0.07				
Class C 1-5 years (715)	1	0.13			2	0.27
Class D 5 plus years (177)	3	1.69				
Class E "Accidental" (1,506)	5	0.33				
Class F Not known (970)	2	0.20	1	0.10	1	0.10

TABLE VII. INCIDENCE OF CONGENITAL DEFECTS* IN RELATIONSHIP TO CONCEPTION-EFFORT TIME

CONCEPTION-EFFORT TIME	CONGENITAL DEFECTS			
	MAJOR DEFECTS		MINOR DEFECTS	
	NO.	%	NO.	%
Class A 1-3 months (3,338)	22	0.62	5	0.11
Class B 3 months-1 year (1,326)	9	0.67	2	0.15
Class C 1-5 years (715)	2	0.27	3	0.41
Class 4 5 plus years (177)	4	2.25	–	–
Class E "Accidental" (1,506)	10	1.26	4	0.26
Class F Not known (970)	14	1.44	1	0.10

*Includes fatal and nonfatal defects.

Comment

In attempting to find clues concerning conception-effort time which might aid in identifying women who have disproportionate pregnancy wastage, we searched the literature for "norms," for length of time needed to conceive. Practically all such data seem to be concerned with special segments of population; for example, patients attending contraceptive clinics. Our first problem, therefore, was to try to establish "norms" for the general population. This material has been presented on the basis of 5,556 individual pregnancies in which positive information was available. The incidence of sterility study in this group is also presented (Table I).

Our original idea of using menstrual-cycle and conception-effort time data in relationship to what happens in various sequences of the outcome of pregnancy remains to be analyzed in the future as more data are acquired.

We were led to believe on a screening analysis of the first 1,500 relationships between conception-effort time and outcome of pregnancy that such data

might give specific leads to identifying patients who would have disproportionate pregnancy wastage without the necessity of having sequences of pregnancy, for the individual patients, available. Specifically, in this screening group, the full-term infants in Class B (3 plus months to one year) conception-effort time showed approximately a 15 per cent smaller survival rate than the full-term infants from the Class A (1 to 3 months) conception-effort time group. As has been shown (Table II), however, this trend did not hold up.

One possible explanation of the failure of this trend to be maintained may concern the very obvious fact that, to date, we have not broken down our data into age groups. Common sense indicates that a conception-effort time of over a year in a 20-year-old would be of much more potential significance than such a conception-effort time in a 40-year-old woman. We feel we should have data on more individual pregnancies before we attempt to interpret age significance, since presently many categories of outcome of pregnancy to conception-effort time relationships would be too small to have any meaning. We are, therefore, continuing the study, hoping that, in the future, a larger accumulation of data will allow analysis in some manner that may be statistically significant.

Pregnancies in which the conception-effort time was over 5 years in general seem to show a possibly significant increase in pregnancy wastage, although, again, age eventually must be considered. The actual number of cases in this conception-effort time class will always be relatively small and it may be necessary to project them by statistical techniques in order to make proper comparisons with the other numerically greater conception-effort time classes.

The high percentage of sterility studies in the Classes C and D, with, perhaps, intensified prenatal attention because of the very nature of the cases, will also need due consideration.

We would like to call attention to the division of abortions into the classes of proved, probable, and possible. We feel such a breakdown is quite essential in a study of this nature. There seems to be a possible trend in the proved-abortion category (Table V) since there is an apparent increase in incidence of abortion as the conception-effort time lengthens. A continuance of this trend might prove statistically significant and may eventually be a point of importance in prognosticating the outcome of future pregnancies.

The findings in ectopic and abdominal pregnancies as well as hydatidiform mole deal with rather insignificant numbers (Table VI). The relatively high incidence, however, of ectopic pregnancies in the 5 plus year conception-effort time group is interesting. The incidence of major congenital defects (Table VII) in this same conception-effort time group may also be significant.

We are not in a position to draw conclusions from this preliminary report on the relationship of the outcome of pregnancy to the conception-effort time. We hope, however, that this report may stimulate interest in this approach to the subject of pregnancy wastage and may possibly encourage other workers to explore its possibilities.

I wish to acknowledge the cooperation of the Bureau of Nursing, Department of Health, Syracuse, New York, in this study.

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Discussion

DR. A. W. DIDDLE, Knoxville, Tenn.—We have also conducted a survey of factors which may be related to abortion: (1) the patient's age, (2) the conception-effort time, and (3) other variables.

Information concerning the relationship of the patient's age to the outcome of pregnancy was available for 1,917 pregnant women. Half of these women were wives of military personnel seen consecutively in 1942-1944. The other half were private patients seen from 1949 to 1954. All were followed past the sixteenth week of pregnancy, and most of them to term. Less than 8 per cent experienced fetal wastage. Forty per cent were multigravidas, each of whom had had one to eight previous pregnancies, and 60 per cent nulligravidas. The ages of the patients in the two groups were comparable.

Unintentional fetal wastage was less common among the younger than among the older women. There was a gradual increase from 5 per cent for those less than 21 years of age to more than 33 per cent for those 40 years old or more. Those who had repeatedly aborted more often lost a subsequent pregnancy than did those who had never experienced abortion. Results indicated, however, that the probability of obtaining a viable baby improved with succeeding pregnancies for those who had suffered previous abortions and who were anatomically normal.

Before we leave this subject, it should be stated that the number of patients in each age group varied; thus, the conclusions reached might not stand up under larger statistical studies.

The conception-effort time was known for 1,550 pregnancies. More than two-thirds of the nulligravidas became pregnant in six months, another 15 per cent in six to twelve months, and still another 11 per cent in two years. Nearly 5 per cent became pregnant after five years or more. The corresponding percentages for the multigravidas were 50, 16, 20, and nearly 1.5. In other words, most patients conceived within one year, regardless of parity. Up to this point our studies agree closely with those of Dr. Schoeneck. We found, however, no significant difference in the conception-effort time between those women within each age group who aborted *intrauterine* pregnancies and those who did not abort such pregnancies. Most of 19 patients with *ectopic* gestations, however, gave a history of conception-effort time of over four years. A comparable observation has been made by Asa Newsom, Jr. (personal communication) in approximately 100 women with extrauterine pregnancies.

Guttmacher (J. A. M. A. 140: 1265, 1949) observed that those gravid patients whose conception was delayed were more likely to abort than those with the shorter conception-effort time. It was suggested that the same process which caused the delay might have caused the abortion. At this reporting, it is my opinion that an important variable affecting this result is the age of the patient.

Finally, it is apparent from Baird's (New England J. Med. 246: 56, 1952) socioeconomic, obstetric study that the well-to-do tend to be healthy and well grown, but that they often reproduce late and to a lesser degree (because of aging) than do the poorer classes, who frequently reproduce early and with much inefficiency because of impaired growth and health. It is my clinical impression, both from observation and from statistical fetal mortality studies, that impaired health may be one of the important reasons that there are twice as many premature births among indigents of long standing as among nonindigent patients, hospitalized in some of the counties of east Tennessee. The indigents not uncommonly have

their health impaired by a poor qualitative and quantitative intake of food. Although there have been no studies made showing the correlation between abortion and the nutritional state of the patients in the communities mentioned, a survey made by the Departments of Nutrition and Agriculture at the University of Tennessee (Southern Cooperative Series Bulletin 20, November, 1951, and personal communication from Dr. F. L. Macleod) indicates that the caloric content and quality of food taken by persons in certain east Tennessee areas are dependent in large measure on the socioeconomic status of the family.

DR. FREDERICK J. LYNCH, Boston, Mass.—In all discussions referable to the problem of pregnancy wastage, attention should be focused on the large number of fertilized ova that disintegrate and are lost in the very early stages of fetal development—so soon that in the great majority of cases there is no clinical evidence of their presence, such as amenorrhea, nausea, or other preliminary manifestations. This extreme wastage is difficult to reconcile with the usual wise economy of Nature, which seldom makes mistakes.

Interest was first focused on these very young abortuses by the work of Corner and Hartman in studying young embryos in the macaque monkey. They called attention to the fact that between 30 and 40 per cent of fertilized eggs suffer prenatal death.

In about 12 per cent of all women who are considered to be pregnant, interruption of the pregnancy is recognized from the usual signs of profuse bleeding and possible discharge of products of conception. The remaining terminations of pregnancy occur so early in fetal life that there may be nothing to call attention to the presence of a fetus except an unusually profuse period.

The reason for this surprisingly high percentage of pregnancy wastage is now one of the prominent problems of the research workers in the fields of human and animal investigations. The older workers felt that the difficulty lay entirely within the uterine cavity, and that the main factor was an inhospitable, unsuitable, or pathological environment for the nidated ovum.

That the uterine factor was the principal cause of pregnancy failure was first questioned by Corner, who studied 1,000 pregnant uteri of swine. In this study it was shown that many of the embryos developed with abnormalities, many died early in the pregnancies, and many progressed normally to term; combinations of these varieties were found in the same uteri. The uteri proved to be normal in so far as the endometrium and progestational activity were concerned, but, in spite of this, death of the ovum and abnormalities occurred. This seemed to indicate that the principal defect must lie, not in the environment provided by the host, but in the genes—egg or sperm. Hertig and Rock have studied 36 fertilized human ova which they recovered from fertile patients, and reported that 40 per cent showed some form of abnormality.

One opinion which is held by many observers is that gamete age (''stale egg'') at the time of fertilization may be one of the important factors in causing early fetal death or developmental abnormalities in the offspring of healthy mothers. The progress of pregnancy following the fertilization of aging eggs was observed by Blandon and Young in a series of cases utilizing guinea pigs as the experimental animal. It was found that, as the length of time between ovulation and insemination increased, the percentage of fertile inseminations was lessened, and after a lapse of 32 hours no eggs were fertilized. Of equal interest was the observation that, as the interval between ovulation and insemination lengthened, the percentage of abnormal development in the eggs that were fertilized increased. After a period of eight hours the percentage of abnormalities was definitely higher, and after a lapse of 26 hours before insemination no normal pregnancies were found.

Soderwall and Young also carried out a complementary investigation of the capacity of the aging spermatozoa to fertilize. This was done by inseminating guinea pigs artificially at varying intervals prior to estrus. It was found that, as the interval was increased, the number of fertile inseminations decreased, to the point of being absent after an interval of 23 hours. An important difference in the utilization of aging spermatozoa was the fact that, although fewer eggs were fertilized, there was no increase in the number of abortions or fetal abnormalities. Apparently if the aging spermatozoa succeed in fertilizing the ovum, unless other factors are present, the development is normal.

The fact that in some animals mating usually occurs only during the definite estrual period, and that in others the ovulation is produced by copulation would make it appear that the sperm should be available to the egg at the immediate time of ovulation. In the various groups of animals studied, however, there has been found a reproductive deficiency of 50 per cent, the great bulk of which is due to death of the embryo and a very small percentage to failure of fertilization.

The problem as to whether this embryonic death may arise from defects of the egg or the sperm, or whether it is caused by faulty genital environment in which the fertilized egg must develop, is also being investigated in domestic animals. Newly ovulated eggs and early embryos are being transplanted from females of low fertility into females of high fertility and vice versa, in an attempt to see if factors contained within the fertilized egg and those involving uterine nidation can be separated.

As Corner has also pointed out, there is, in addition to the inherent defects of the early embryo, the possibility of nutritional deficiencies, toxic and febrile conditions, and disturbed endocrine function in the mother, which may cause aberrations of the maternal environment that could bring about defective embryonic development and prenatal death.

Many obstetricians have, by a process of trial and error, worked out an endocrine program for the treatment of sterility and repeated abortions, in an attempt to improve the character of the impoverished endometrial soil prior to nidation and to nurture the implanted ovum in its very early life. Hughes and his associates have approached the problem from the point of view of faulty nidation environment, which may be a factor in the patients who show a prolonged conception-effort period. They have found that patients who complain of sterility, in whom biopsy shows that the endometrium is not progressing to a good progestational stage, can be benefited materially by the administration of 0.1 mg. of diethylstilbestrol daily for 12 days following the completion of the menstrual function, and then 25 mg. of progesterone a day for the ensuing six days. He has found by endometrial biopsy that an endometrium of the full secretory type may be produced after pursuing this routine for a varying period of months, and reports successful pregnancies in women who had previously been sterile or had early abortions. Although this endocrine treatment may be particularly applicable to the group who have had repeated abortions, it is appreciated that in many of these cases with defective endometrium, spontaneous improvement may take place.

Speert reports a series of 121 patients with a primary sequence of three abortions, 81 per cent of whom were carried to viability in a fourth pregnancy without the administration of hormones.

Bevis thinks that much of the success achieved in patients with a history of successive abortions is due to the patient's confidence in her obstetrician. He feels that psychogenic factors play an important part in this aberration of reproductive function, and therefore that psychotherapy has an important place in its treatment.

DR. E. C. HUGHES, Syracuse, N. Y.—I would like to discuss the papers of Drs. Randall and Schoeneck jointly, because I think they are corollaries in many aspects. I would also like to discuss the Hughes treatment that has been talked about this morning.

I think the points that have been brought out here by Schoeneck's analysis are very important. He is doing an excellent job and will report more pertinent findings. He also hopes that others will make similar surveys on a statistical basis to find out what types of people have these complications of pregnancy. I think that a great deal of importance should be given to a poor obstetrical history, as Randall has also stated. Patients in these categories demand study before pregnancy, and possibly preconceptional treatment. Perhaps we should treat them psychogenically, perhaps nutritionally, or socially, or perhaps by endocrines. We do not claim that we must prime every patient by diethylstilbestrol or other hormones, but we do feel that we must survey them and treat them in some manner prior to a subsequent pregnancy. I'd like to emphasize that point, because I think it is important.

The second point that Randall brought out was the low progestational level in some patients as indicated by the vaginal smear. We have taken vaginal smears by his method. We also have sent them to his laboratory and correlated the results with our hormonal studies

during pregnancy. Some smears have shown a correlation with the pregnanediol excretion of these patients. Some patients who have a low excretion of pregnanediol in the urine during the early months of gestation go through a normal pregnancy. Those patients, however, generally have a relatively high excretion of chorionic gonadotrophin. We have also had patients with a low excretion of pregnanediol who have aborted. These women generally have had a low excretion of chorionic gonadotrophin as well.

There is a synergism between the secretion of chorionic gonadotrophin by the trophoblast and the secretion of progesterone and estrogen by the ovary. If the ovum and trophoblast are good, a large amount of chorionic gonadotrophin is put out and it stimulates the ovary. If the ovary is poor and does not respond to the stimulation, then you still may have a low output of progesterone or a low excretion of pregnanediol, but the patient may go to term. When the situation is reversed and the amount of chorionic gonadotrophin is below the average, but the corpus luteum is highly sensitive, the latter may put out enough steroid to keep the decidua going.

We have 68 patients who have been treated prior to conception with diethylstilbestrol, with or without progesterone, until the endometrial function, as proved by four or five endometrial biopsies, has been adequate. After pregnancy has occurred in these patients, we have noted that the secretion of chorionic gonadotrophin by the trophoblast is generally a little higher than in the normal pregnant patient, or at least approaches the high normal. We have had some patients who have secreted as much as 80,000 units of chorionic gonadotrophin (one unit corresponds to 3 international C.G. units). We feel that if we have prepared the endometrium properly the chorion grows a little faster and a little better, and puts out increased amounts of chorionic gonadotrophin.

We are sure that diethylstilbestrol is not the entire solution to the problem. At present we are carrying out the following experiment: We have two products, product A, which contains 0.1 mg. of diethylstilbestrol, and product B, which is a placebo. I myself do not know which one contains the diethylstilbestrol. We are treating 16 patients with A and 16 with B simultaneously. Biopsies have been taken at the same intervals in both groups and have been sent to the same laboratory, where the staining and cutting are done by the same method. They are now being evaluated by several of our pathologists. We want to see whether it is diethylstilbestrol, the biopsy, or something else which creates the more active endometrium that is noted after such treatment.

In any event, we plead for more adequate study of these patients before pregnancy—even those who have had only *one* abortion, *one* premature labor, or *one* congenitally malformed child. We hope the patterns that Schoeneck and Randall have explained to us will give us the clue to proper study and treatment prior to pregnancy.

STUDIES ON THE MECHANISM OF AN ECLAMPSIA-LIKE SYNDROME IN RATS*†

ERNEST W. PAGE, M.D., AND MARY BETH GLENDENING, PH.D.,
SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology, University of California School of Medicine, San Francisco)

THE production of a syndrome in rats resembling in many respects the toxemia of human pregnancy was described in 1951 by Masson, Corcoran, and I. H. Page.[1] It was accomplished by giving subcutaneous injections of renin for several days to rats which had already been made hypertensive with a high sodium intake and the administration of desoxycorticosterone acetate (DCA). The majority of such animals continued to drink 1 per cent sodium chloride solution despite a severe oliguria, developed massive generalized edema and severe proteinuria, a further rise in blood pressure, and, in some instances, convulsions and death.

The outstanding pathologic lesions, described by the same authors,[2] consisted of diffuse, small hemorrhages in the brain, intestinal tract, adrenal glands, and kidneys; capillary thromboses in various organs; a thickening of the glomerular capillary walls due largely to a swelling of the endothelial cells; and a dilatation of the tubules which were filled with hyaline, granular, and pigment casts. These lesions could be produced by substituting hourly intraperitoneal injections of angiotonin in place of the renin,[3] or by substituting cortisone[4] or hydrocortisone[5, 6] in place of the DCA. No part of the syndrome can be reproduced if rats are given water instead of sodium chloride solution.

Although the resemblance between this experimental syndrome in rats and human eclampsia may be fortuitous, we have studied the syndrome since 1951 with the particular aim of learning what similarities there may be and what factors are responsible for the development of the generalized edema.

Methods

The methods employed were quite similar to those utilized by Masson and his co-workers. "Sodium-DCA disease," first described by Selye, Hall, and Rowley[7] in 1943, was induced in uninephrectomized rats by implanting 60 mg. of DCA under the skin of the neck, either in the form of 30 mg. discs or 15 mg. cylinders.‡ The animals were then placed in metabolism cages and 1 per cent sodium chloride solution was substituted for the drinking water. The diet, high in protein, consisted of Purina fox chow, casein, and added vitamins. Body

*This investigation was supported by grants from the National Heart Institute, National Institutes of Health; and the Christine Breon Fund. Mr. Leonard Olson gave valuable technical assistance.

†Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

‡Desoxycorticosterone acetate powder and cylinders were generously supplied by Dr. Ernst Oppenheimer of Ciba, Inc. Dr. G. M. C. Masson kindly prepared the 30 mg. discs. The two forms appeared to be equally effective.

weight, fluid intake and output, urinary protein (Purdy method), and systolic blood pressure were determined at regular intervals. The blood pressure was determined on the tail by the use of a special microphone, as described by Friedman and Freed.[8] The renin used was prepared from desiccated hog kidney (Viobin), and was derived from Fraction C described by Schales.[9] The total amount of renin solution given was 4.5 ml. in three divided doses 4 hours apart. The effective quantity of renin administered to one rat varied from 22 to 97 "rabbit units." (One unit, as defined by Schales and Haynes,[10] is the amount needed intravenously per kilogram to raise the blood pressure of an unanesthetized rabbit 30 mm. Hg.)

For the measurement of renal vein flow, we resorted to the method described by Dock[11] because some of our animals were almost anuric and conventional clearance techniques could not be employed. The quantity of renal vein blood flowing into a 1 ml. horizontal pipette was measured during the first 30 seconds after puncture. The values are not comparable to those obtained by PAH or Diodrast clearance methods in undisturbed rats because of operative manipulations and vessel ligations prior to measurement, but were sufficiently consistent to compare one group of rats with another.

The body weights of normal rats rarely fluctuate more than 5 per cent from one day to the next. A weight gain of 10 per cent in 24 hours was therefore considered significant from the standpoint of edema formation. The average systolic blood pressure in rats is 110 mm. Hg, and levels above 140 were considered hypertensive.

Results

The various groups of animals may be described under six headings, and Figs. 1 to 6 typify the results in each. Values shown in the diagrams are the median values for each item in groups of 10 or more rats, whereas the ranges and statistical evaluation are given in the text below.

Normal Controls (Fig. 1).—Normal uninephrectomized rats consume from 10 to 30 ml. of water per day, and excrete from 6 to 20 ml. of urine containing minute quantities of protein which vary with sex and species. Although the systolic blood pressures range from 90 to 125 mm., the pressure is fairly constant for any one animal. The mean renal vein flow as determined on 10 rats was 3.37 ml. per minute per gram of kidney. This is twice the flow observed by Dock (possibly because we substituted 18 gauge for the 20 gauge needles used in the original method), but is only half the value calculated from reported PAH clearances obtained in unanesthetized, undisturbed rats.[12]

Effects of Renin on Normal Rats (Fig. 2).—When renin is given subcutaneously to normal rats, a diuresis and proteinuria result, and there are moderate rises of blood pressure. After repeated injections, the animals lose weight. At no time are generalized edema or vascular lesions observed. When 1 Rb. U. of renin is injected intravenously, the renal vein flow is reduced to a mean of 2.55 ml. per minute per gram (12 animals), but this reduction of 0.82 compared with the standard deviation of 1.38 is not statistically significant.

The diuresis and proteinuria induced by renin have been studied by several groups of workers[13-17] without ascertaining the exact mechanism. Both effects are known to result from the angiotonin formed by the renin, and the proteinuria is due in part, if not entirely, to an increased permeability of the glomerular capillaries to plasma.

The Effects of Sodium Chloride (Fig. 3).—When 1 per cent sodium chloride is substituted for the drinking water, the fluid intake and urinary output are moderately increased, but there is no change in body weight or proteinuria. After two or three weeks there is a slight rise in blood pressure, but rarely to

hypertensive levels. It has been shown by three groups of workers[18, 19, 20] that increasing the sodium chloride concentration still further will result in true hypertension. Meneely and associates[20] showed that, after one year on various sodium intakes, there was a linear relationship between the systolic blood pressure and the concentration of sodium in the diet. When the latter reached as high as 7 to 9.8 per cent, 18 per cent of the animals developed gross, generalized edema and renal failure due to severe renal lesions. This supports the thesis that DCA only facilitates the damaging effects of sodium given at lower levels. Rosenman, Freed, and Friedman[21] have demonstrated that an adequate intake of potassium is essential for these sodium effects, and that, with restricted potassium, an excess of sodium produces a depressor rather than a hypertensive effect.

Effects of Sodium and DCA (Fig. 4).—When desoxycorticosterone acetate is given, all of the effects of sodium are intensified. Within one or two weeks blood pressures rise to hypertensive levels so long as the ingestion of saline continues. The fact that DCA alone produces no disturbance so long as the rats drink only water indicates that it is the sodium ion and not the steroid which produces the damage. There is a moderate increase of proteinuria (70 to 270 mg. per 24 hours), and the fluid intake and output become tremendous. Daily urinary volumes vary from 90 to 330 ml., in some instances exceeding the body weight. Arterial disease develops, as evidenced by arteriolar and glomerular lesions, but, despite this, the kidneys are able to excrete the sodium load and generalized edema does not develop except in a few animals in the terminal stages of sodium-DCA disease. The mean renal vein flow in 10 rats with sodium-DCA disease was 1.94 ml. per minute per gram, a significant reduction of 1.43 ml. ± S.D. 1.3 from the normal control value ($p = 0.03$).

Effects of Sodium, DCA, and Renin (Fig. 5).—When the three subcutaneous injections of renin are given to rats with sodium-DCA disease, an acute disturbance often follows which bears many similarities to human eclampsia. The first event in about half of the animals appears to be a sharp decrease in the urinary output with a considerable increase in the concentration of protein in the urine. This occurred in 50 out of 110 rats, whereas the remaining 60 animals responded like normal rats with an increased output. Oliguria developed more often when the effective dose of renin was high. The median values illustrated in Fig. 5 are from the 50 animals responding with oliguria.

Despite the reduction of urinary output, the rats continued to drink considerable amounts of saline and 32 of the 50 animals had significant gains of body weight due to generalized edema. Fig. 7 shows a rat 24 hours before and 24 hours after the renin injections, with a gain of 45 per cent of its body weight. Such an animal is lethargic, but when touched responds with convulsive twitches. Spontaneous convulsions or death were rare in our series, probably because the administration of renin was limited to one day.

When one rabbit unit of renin was given intravenously to rats already sensitized by sodium and DCA, the mean renal blood flow was only 1.0 ml. per minute per gram. This is a statistically significant reduction from the lowest of all other groups measured ($p = <0.01$). Such a finding is in keeping with the reduced urea clearance noted by Masson and co-workers[1] and with the reduced PAH and creatinine clearances reported by Gaunt and Renzi.[22]

We have been unable to precipitate the eclampsia-like syndrome in sodium-DCA sensitized rats by substituting for renin the following substances: Pitressin, epinephrine, thromboplastin, ACTH, histamine, or various human placental extracts. The course of normal pregnancy in 12 rats with sodium-DCA disease was not marked by any edema or exacerbation of hypertension.[23] Heating the renin solution to 65° C. for 15 minutes to destroy its enzymatic properties also

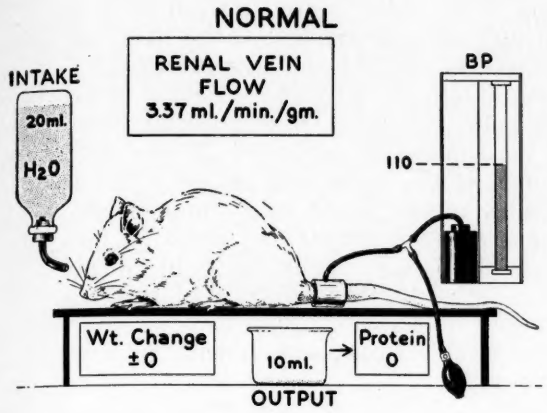


Fig. 1.

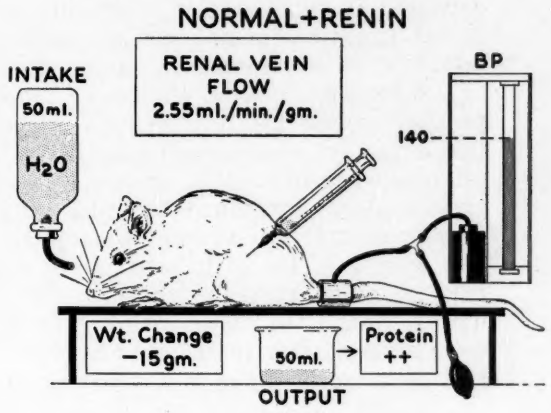


Fig. 2.

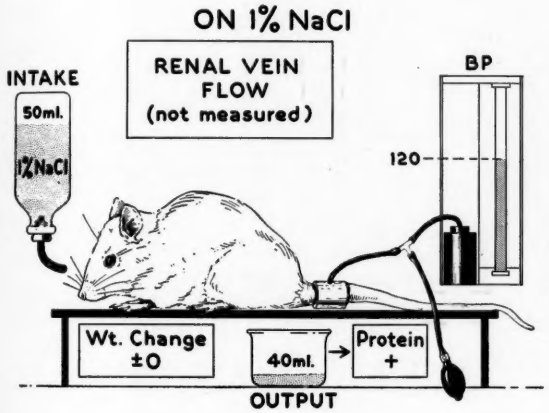
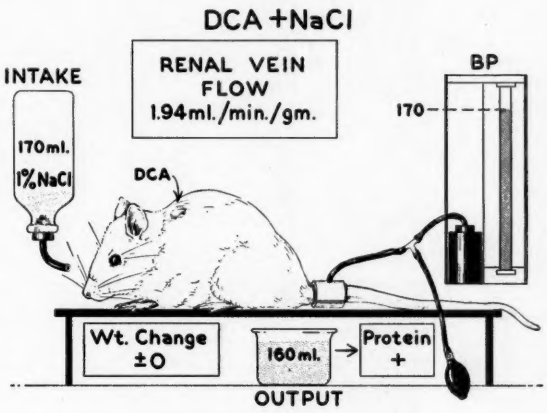


Fig. 3.



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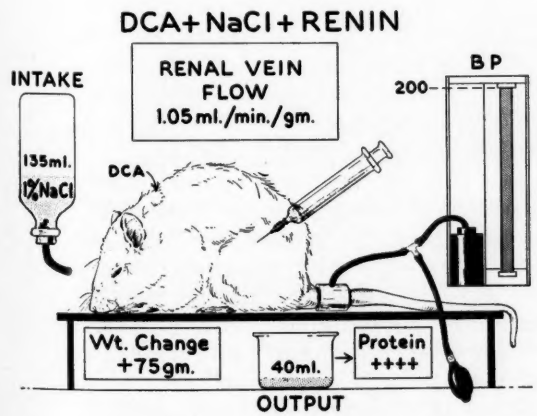

Fig. 5.

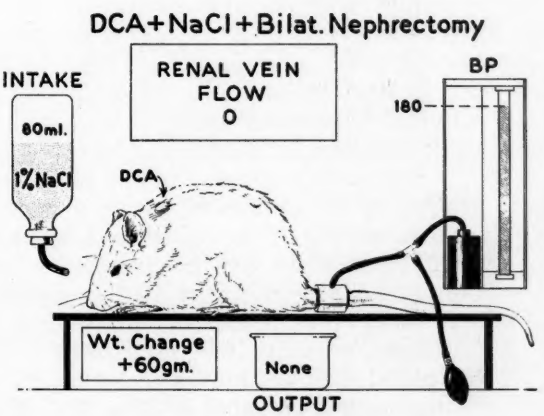

Fig. 6.

rendered it impotent for producing edema. The prior administration of mercurial diuretics did not prevent edema formation after renin, but the prior administration of Apresoline, as described by Gaunt and Renzi,[22] was successful.

Effects of Sodium, DCA, and Total Nephrectomy (Fig. 6).—Because of the possibility that the intense renal ischemia with reduction of glomerular filtration after renin was the prime cause of the edema, we subjected 13 rats with established sodium-DCA disease to a removal of the remaining kidney. Six of these animals continued to drink appreciable quantities of saline and became grossly edematous, whereas the remaining 7 stopped eating and drinking and lost weight. This is different from the results of total nephrectomy in normal rats, all of which stop drinking. It also differs from the behavior of the rats with sodium-DCA disease studied by Mills and Rodbard.[24] Their rats, however, were offered after total nephrectomy a choice between sodium chloride solution and dextrose in water and wisely chose the latter.

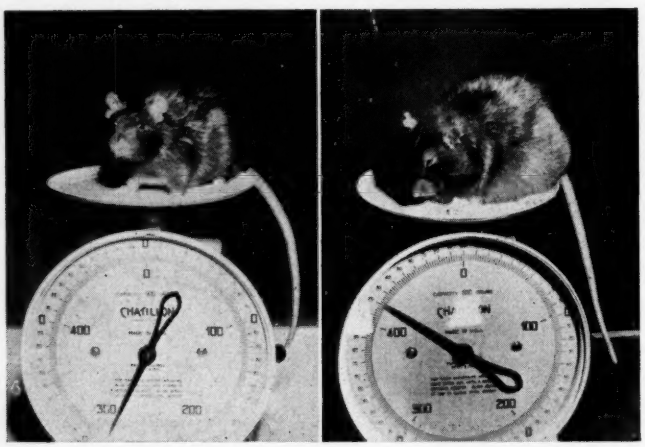

Fig. 7.—Photographs of the same rat 24 hours before (left) and 24 hours after (right) the injection of renin. Note the weight gain of 130 grams due to edema.

Pathologic Findings

At autopsy, rats with sodium-DCA-renin disease showed edematous subcutaneous tissues due in part to the accumulation of a hyaluronate gel which disappeared upon in vitro treatment with hyaluronidase. There were varying degrees of ascitic and pleural fluid, and multiple small hemorrhages in the intestinal tract, adrenal glands, and kidneys. (The brains were not examined in this series.) Microscopic sections of the kidneys and heart were stained with the colloidal iron-Schiff reagent described by Rinehart and Abul-Haj[25] in order to study changes in the mucopolysaccharide ground substance.*

The earliest change in the glomerulus is a thickening and granular disintegration of the epithelial portions of the basement membrane, with avascularity and narrowing of the capillary lumina. At this stage, the tubules are relatively unaffected except for the presence of protein casts. In more advanced lesions, the epithelial structures of the glomerular wall disintegrate, leaving swollen, laminated endothelial elements with intracapillary fibrin deposition and leakage of plasma proteins into the capsule. Fig. 9 shows such a change, and should be compared with the normal rat glomerulus shown in Fig. 8. Some of the tubular changes are illustrated in Fig. 10. The dilated tubules are filled with hyaline, granular, and pigment-containing casts originating from inspissated plasma

*We are indebted to Mr. S. K. Abul-Haj for the special preparations and for photomicrographs in color.

which has leaked through the glomeruli. The tubular epithelium shows some desquamation and loss of the brush border and there are a few scattered petechial hemorrhages. Such findings are noted in eclampsia, but are also present in the so-called lower nephron nephrosis.

Lesions of the blood vessels and of the ground substance are found in practically every organ. In the heart, each muscle fiber is normally surrounded by a delicate mucopolysaccharide membrane. In sodium-DCA-renin disease, there are an extensive swelling and disintegration of these membranes resulting in varying degrees of necrosis of the muscle fibrils. The mucopolysaccharide (ground substance) material of arterial walls is markedly thickened and there are deposits of fibrin and other plasma proteins in and below the intima (Fig. 11).

Fig. 8. Fig. 9.

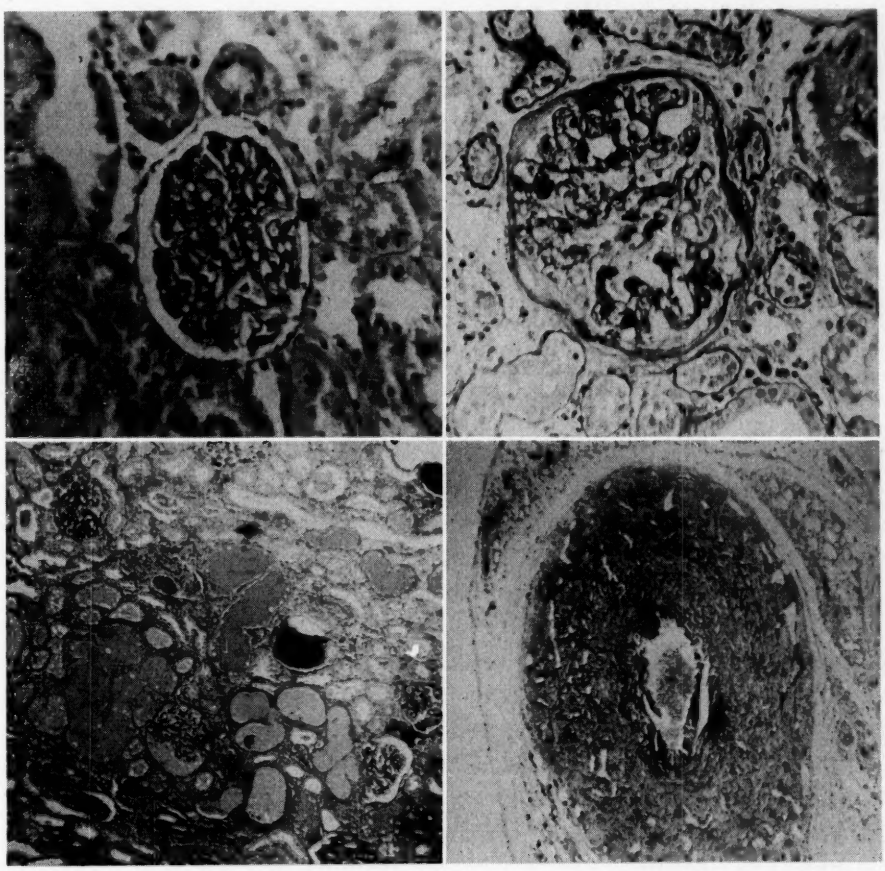

Fig. 10. Fig. 11.

Fig. 8.—Normal rat glomerulus. (Colloidal iron-Schiff stain.)
Fig. 9.—Glomerular change due to sodium-DCA-renin disease. (Colloidal iron-Schiff stain.)
Fig. 10.—Renal tubular changes in sodium-DCA-renin disease. (Colloidal iron-Schiff stain.)
Fig. 11.—Arterial wall changes due to sodium-DCA-renin disease. (Colloidal iron-Schiff stain.)

While many of these lesions can be found in fatal eclampsia they are not specific and the similarities might be coincidental. The basic pathology of sodium-DCA-renin disease appears to be a depolymerization of supporting con-

nective-tissue ground substance, and a seepage of fibrin and other plasma elements into the swollen mucopolysaccharides with ultimate breakdown of the protective barriers of ground substance. This results in a necrosis of the cellular elements contained within these disrupted barriers.

Comment

The subcutaneous injection of renin normally leads to diuresis, and this was also observed in slightly over half of the animals sensitized with sodium and DCA. The greater the degree of sensitization and the larger the dose of renin, the greater is the likelihood of oliguria and generalized edema. Neither the oliguria following renin nor the anuria following total nephrectomy leads to edema, however, unless thirst is maintained, with a continued intake of saline solution. Sodium and DCA may alter the electrolyte distribution within osmoreceptor cells in such a way as to maintain thirst.

The fact that mercurial diuretics fail to prevent edema after renin, whereas Apresoline succeeds, focuses attention upon the vasoconstrictor effects of renin. The work of Gordon, Drury, and Schapiro[26] supports the premise that excess sodium sensitizes blood vessels to the action of circulating pressor substances. We believe that renin, by its constricting action on the sensitized renal arterioles, reduces blood flow and glomerular filtration and creates a glomerulotubular imbalance with respect to the secretion and reabsorption of water and sodium chloride.

The successful production of gross generalized edema in rats by the method described apparently depends upon the simultaneous operation of the following factors: (1) an increased rate of sodium reabsorption by the renal tubules induced by the DCA; (2) the obligatory consumption of sodium chloride solution for the relief of thirst; (3) the persistence of thirst despite a reduced or even absent urinary output; (4) a sensitization of the renal arterioles (by the first two factors) to the vasoconstrictor action of angiotonin; and (5) a decrease in renal blood flow and glomerular filtration rates leading to a glomerulotubular imbalance.

These five factors may now be considered in relationship to the generalized edema which accompanies the toxemia of pregnancy. Although the results of experiments on rats can never be transferred directly to women, there are certain parallel circumstances between sodium-DCA disease and pre-eclampsia which merit discussion.

In women, normal pregnancy is accompanied by a progressive increase in the placental production of sodium-retaining steroids. In rats, the pellets of DCA were the counterpart of the human placenta in this respect. In pregnant women, the increased sodium-reabsorbing capacity of the renal tubules is normally balanced by a considerable increase in glomerular filtration rates. At the eighth month, for example, the glomerular filtration rates are on the average 70 per cent higher than they are in the same individuals when not pregnant.[27] Any factor which sharply reduces this high filtration rate *without removing the source of excess steroids influencing the renal tubules* will lead to sodium retention. In the rats, this was brought about by renin, but in pre-eclampsia the

agent which brings about the reduction in renal blood flow and glomerular filtration rates is unknown. That such reductions do occur in pre-eclampsia is now documented,[28, 29, 30] although it was not fully recognized until recently because pre-eclampsia rates had been compared to normal nonpregnancy rather than normal pregnancy rates. Bucht and Werko found both the inulin and PAH clearances in toxemias to be more than three standard deviations below the values found for the corresponding periods of normal pregnancy. Our theory[31] is that the chemical mediator operating in pre-eclampsia to produce these effects is of placental origin and results from placental ischemia, but this is not proved.

In women, this sodium retention by the kidneys is followed by edema, provided that the ingestion of sodium chloride continues—as it usually does. In rats, the continued consumption of sodium chloride was obligatory. If they are offered a choice of saline or distilled water, edema does not occur. In this respect, rats are wiser than women, because patients with pre-eclampsia and edema continue to ingest high quantities of sodium chloride unless instructed to do otherwise.

All of the five factors which apparently combine to produce edema in the rats seem, therefore, to have their parallels in pre-eclampsia: (1) the presence of sodium-retaining steroids in excess; (2) the continued ingestion of sodium chloride; (3) the maintenance of salt appetite or thirst despite oliguria; (4) an apparent sensitization of arterioles to a vasopressor substance (true in the rats but theoretical in pre-eclampsia); and (5) a decrease in renal blood flow and glomerular filtration rate leading to a glomerulotubular imbalance in the handling of sodium and water.

Conclusions

1. The eclampsia-like syndrome first described by Masson, Corcoran, and I. H. Page can be readily reproduced by the subcutaneous administration of renin to rats which have first been made hypertensive by the administration of desoxycorticosterone acetate (DCA) and a high sodium intake. The ease with which the entire syndrome of proteinuria, oliguria, marked hypertension, severe generalized edema, and nervous irritability or convulsions can be induced is dependent in part upon the degree of prior senstization with sodium and DCA and the potency of the renin solutions. In this series, only 32 of 110 animals so treated developed the complete syndrome.

2. The most significant pathologic lesion appears to be a depolymerization of the mucopolysaccharide ground substance which makes up supporting connective-tissue structures, and a seepage of fibrin and other plasma elements into and through these swollen structures. The ultimate breakdown of these mucopolysaccharides results in a necrosis of the cellular elements contained within these disrupted barriers.

3. Sodium itself plays the final determinate role in causing the entire syndrome, since the same clinical and pathologic picture can be obtained by prolonged and excessive quantities of sodium chloride alone.

4. Sodium-DCA-renin disease in rats cannot be reproduced by substituting, in place of the renin, epinephrine, Pitressin, thromboplastin, ACTH, histamine,

or crude human placental extracts; nor by inducing pregnancy and parturition. It cannot be prevented by the prior administration of mercurial diuretics but can by the prior administration of hydrazinophthalazine (Apresoline).

5. If rats with established sodium-DCA hypertension are totally nephrectomized and offered only 1 per cent sodium chloride solution to drink, about half of them will continue to ingest the solution and become edematous. Thus the maintenance of thirst after reductions in urinary output appears to be an important factor in causing the edema.

6. Rats with sodium-DCA hypertension were shown to have a reduced renal vein flow. The injection of renin into such animals produces a much greater and highly significant reduction of renal vein flow. Such reductions are minimal when renin is given to normal rats. Thus the sodium and DCA treatment literally sensitizes the renal blood vessels to the vasoconstrictor action of angiotonin. Renin given to normal rats produces a diuresis. When it produces oliguria in the sensitized rats, we believe that it is because of the sharp reduction in glomerular filtration which creates a glomerulotubular imbalance in the handling of water and sodium chloride.

7. The clinical implications of these experiments are discussed. At least five factors operate together in the rats with sodium-DCA-renin disease to produce generalized edema. There are five parallel factors which may operate in a similar fashion in human pre-eclampsia.

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Discussion

DR. RUSSELL R. DE ALVAREZ, Seattle, Wash.—Dr. Page has presented another step in the investigation of the possible causes of the perplexing syndrome of pre-eclampsia-eclampsia. All who have investigated endocrine effects and studied water metabolism and electrolyte patterns in toxemia of pregnancy are aware of some of the end results of electrolyte and water manipulation. Some underlying feature, such as arteriolar vasoconstriction, however, must play a basic role in producing such results. While the sites and the effects of such vasospasm are well known, its exact etiological mechanism still eludes explanation, except for the possibility that the placenta is probably the initiating influence.

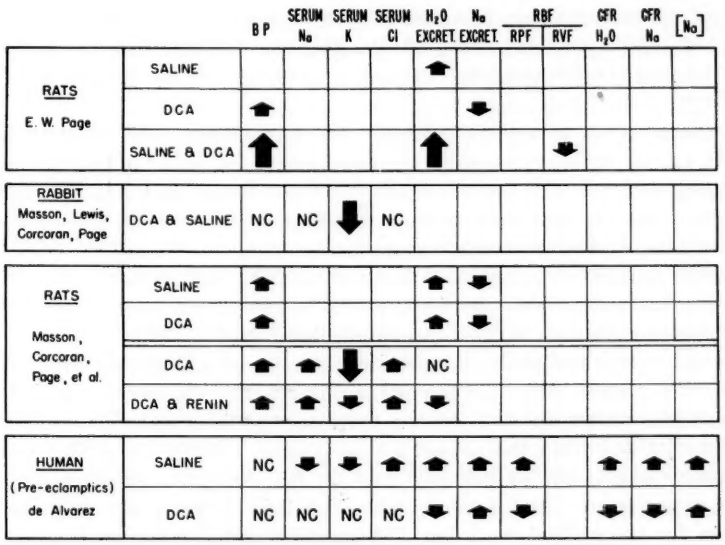

Fig. 1.—Effects of saline and DCA on electrolytes and renal hemodynamics.

Dr. Page has shown that some of the clinical, physiologic, and even pathologic manifestations of pre-eclampsia-eclampsia may be induced in carefully prepared nonpregnant rats and even in male rats. In pregnant rats, however, the superimposition of sodium-DCA influence does not provoke the "disease," either clinically or physiologically. Does this mean, then, that the steroids elaborated by the placentas of rats are different from those elaborated by the placenta of the human patient, who is properly "sensitized" by the proper electrolyte, in the proper medium, and in the proper concentration? Or does it mean that placental adrenocortical-like steroids are suppressed by DCA? The mechanism by which the "toxemia of pregnancy" syndrome is produced in rats depends principally upon the prolonged administration of sodium chloride, with attendant sensitization of arterioles to the action of vasopressor substances. DCA, representing the placental counterpart in the nonpregnant animal, further enhances the effect of sodium chloride. Dr. Page has stated that renin, the vasoconstrictor, reduces glomerular filtration as well as renal blood flow, this reduction in glomerular filtration is a relatively common occurrence in pre-eclampsia-eclampsia.

Similar explanations for the development of pre-eclampsia-eclampsia may be applied to the human pregnant patient on theoretical grounds. In normal pregnancy the placenta, by elaborating an excess of most of the known steroids, induces an increased renal tubular

reabsorption of sodium. The maximal tubular reabsorption capacity for sodium is also increased during normal pregnancy. With the known increase in the glomerular filtration rate, a perfect stage is set for the development of pre-eclampsia-eclampsia. Alterations in any of these features should theoretically produce eclampsia. They do not uniformly do so, since all features necessary for the development of the syndrome are not altered simultaneously in all patients. Thus, in the human patients, as in the experimental animal, certain biologic specificity also may exist.

Among patients with severe pre-eclampsia whom we have studied, our regimen of therapy effected complete clinical and laboratory reversal to normal. One group of these patients, after control of the toxemic manifestations, was then placed on a regimen of forced fluids alone; another group, on forced fluids plus sodium chloride; while the third group was given forced fluids plus sodium bicarbonate. The administration of abundant fluids alone did not reproduce the manifestations of pre-eclampsia. The sequence of events among the other two groups was as follows: sodium retention, water retention, weight gain, edema, and hypertension. Even though we did not continue these regimens to determine whether albuminuria occurred or increased, fine twitches were noted in one patient. That vasoconstriction, renal and otherwise, is a common feature in the patient with toxemia of pregnancy is an established fact, but we are still searching for its cause. A question which might well be asked of Dr. Page is whether sodium chloride is specific in producing the toxemia-like syndrome in rats, or whether sodium in any form will provoke the same picture.

When DCA is given to saline-"primed" human patients with toxemia of pregnancy, a few, but not all, of the changes noted in rats occur; the same is true when saline alone is given to human patients with pre-eclampsia. In considering the immediate effects of these agents and comparing the responses in human beings with those of subprimates, one notes (Fig. 1) similarities, dissimilarities, or no change.

Even though convulsions are rare in rats sensitized by sodium and DCA, DCA and renin are known to depress serum calcium. Since this is so, could not such a depression have provoked the convulsive manifestations in the rat depicted in Fig. 7?

Any discussion of blood-pressure determinations in animals should give scrutinizing attention to the method used. We have found the photoelectric tensometer method of determining blood pressure superior to that of the volumeric plethysmographic method, with more uniform results obtained when the animal's paw is used. While the actual numerical value of blood pressure alone is not of primary interest, the change in pressure is the significant feature. The accuracy of blood-pressure determinations depends not only upon adherence to rigid criteria for the method used, but also upon the influence of anesthesia, the animal's temperature, and the animal's familiarity with the procedure.

Renal vein flow is a satisfactory substitute for determining renal blood flow only if it is coupled with a consideration of renal arterial flow, with simultaneous measurements of afferent blood and its composition and efferent composites and metabolites. Dock found that the rate of renal vein flow per gram of renal tissue in hypertensive rats was the same as that in rats without hypertension following unilateral nephrectomy.

The histologic findings in various organs of these treated rats are intriguing. Just as the pathologic picture in our patients with eclampsia may be one of complete normality, one of generalized edema and cloudy swelling, one of lower nephron nephrosis, or one of the so-called "typical" histopathology, so does Dr. Page conclude that the histologic pattern of the eclampsia-like syndrome in rats is also not pathognomonic. Because of the histopathologic variations in human eclamptic patients with identical clinical syndromes, I have often wondered whether more than one type of eclampsia exists. In addition to the hepatic and renal pathology, it would be interesting to know the histologic picture in the various zones of the adrenal cortex among the animals studies by Dr. Page. Inasmuch as the site of origin of the DCA-like compounds is considered to be the zona glomerulosa, one would expect atrophy of the zona glomerulosa, with a pronounced depletion of lipids, following the administration of either saline or DCA or a combination of these substances.

Even though it is not yet possible to pinpoint the cause of the true toxemias of human pregnancy, we are indebted to Dr. Page for an interesting presentation which clearly indicates

that the administration of sodium chloride, DCA, and renin to rats reproduces some of the phenomena found in toxemia of pregnancy.

DR. JOHN C. ULLERY, Philadelphia, Pa.—The etiology of eclamptogenic toxemia has remained an enigma to medicine. During the past two decades intensive investigations, both in the laboratory and in the clinical field, have been made in an effort to find the factor or factors causing eclampsia. Although much progress has been made toward that end, there are still specific areas that need to be evaluated.

Our knowledge of toxemia in pregnancy, however, is increasing steadily. Studies on hypertensive disease, salt retention and the enzymatic effects of certain extracts, and more recently the investigation of the corticosteroids have led us into a better understanding of the more than casual relationship between disturbance of the basic metabolic functions and eclampsia.

The work of Masson and his co-workers in 1950 and this elaboration by Drs. Page and Glendening in their presentation today show that this "sensitization" in rats by sodium and DCA is in reality producing dysfunctions of metabolism and physiology, and thus a conditioned nutritional deficiency. This finding further amplifies the belief that toxemias of pregnancy, including eclampsia in human patients, are basically nutritional deficiency states.

When the five factors listed by the authors in producing this syndrome are noted, support can be given to their thesis that they cause an arbitrary, artificial dysfunction, producing a breakdown of supporting tissues with the ultimate destruction of the protective barriers of ground substances.

Although few of us can discuss the investigative approach to this study, certain clinical implications merit our attention. It is difficult to believe that sodium plays the final determining role in this syndrome, as we know that salt restriction per se in pregnancy is only a symptomatic approach and not the answer to the prevention of eclampsia. On the contrary, it appears to be one of association with the production of edema due to the marked disturbance in water and electrolyte metabolism and the nutritional imbalance which is present.

The fact that this syndrome occurred in only 32 of 110 animals so treated raises the question as to whether or not the genetotrophic theory of Williams is also an important factor in causing eclampsia when associated with the nutritional deficiency state. I believe Drs. Page and Glendening have shown that a breakdown in the many conditions affecting nutritive balance is more and more clearly implicated in the etiology of eclampsia. Their investigations will be of great value in our search for definite answers concerning the etiology of this complex syndrome, eclampsia.

DR. PAGE (Closing).—In answer to Dr. de Alvarez's comments, I can only say that one must be cautious in applying the results of experiments on women directly to rats!

In answer to the specific question concerning calcium, we made no measurements. Masson and Gaunt have both shown, however, that whenever convulsions do occur, there are associated with them petechial hemorrhages in the brain. They attribute the convulsions to these multiple hemorrhages.

Salt retention per se probably sets the stage, and is possibly even a necessary predisposing factor for the development of toxemia. I think we must come to the realization that we are probably dealing with two simultaneously operating factors. One is the sodium sensitization, which can be easily demonstrated in the rats. But, second, something else disturbs the glomerular-tubular balance, which normally is able to keep pace with the sodium load. What this second factor is in women is unknown, but the net effect is to reduce the glomerular filtration rate very sharply in the face of a continued increase in the tubular reabsorption of sodium. If one does not correct the hormonal factors, presumably of placental origin, which have geared the renal tubules to reabsorbing this larger amount of sodium, then any factor which sharply reduces the glomerular filtration rate will lead to sodium retention.

The main thought that I would like to leave with you is that we must have at least two simultaneously operating factors in order to explain the sensitization and massive edema which occur in rats and probably in women.

PLACENTAL TRANSMISSION OF ERYTHROCYTES*

WILLIAM F. MENGERT, M.D., DALLAS, TEXAS, CLYDE S. RIGHTS, M.D., TACOMA, WASH., C. R. BATES, JR., M.D., WICHITA FALLS, TEXAS, AND ALLEN F. REID, PH.D., GERDA R. WOLF, B.A., AND G. COOLEY NABORS, M.D., DALLAS, TEXAS

(From the Department of Obstetrics and Gynecology of Parkland Hospital and the Departments of Obstetrics and Gynecology and of Biophysics of the Southwestern Medical School of The University of Texas)

WITH the establishment of the etiology of erythroblastosis by Levine and his associates[1] in 1941 and with knowledge that the antigenic factor is attached to red blood corpuscles,[2] it became evident we must revise previous concepts of the completely separate integrities of the fetal and maternal blood vascular systems.

Levine[3] believes that erythrocytes can normally cross the placental barrier and that as little as 0.067 c.c. of packed fetal cells can produce immunization. Others have argued that escape of fetal red cells into the maternal circulation is abnormal and takes place as the result of placental defect, or, if there is no defect, at the time of separation. Thus, manual removal of the term placenta or curettage for incomplete abortion might favor introduction of fetal erythrocytes into the maternal circulation.

Dienst[4] in 1905 was among the first to challenge the concept of separate integrities of maternal and fetal circulations when he suggested that a connection between them might play a part in the pathogenesis of eclampsia. Space does not permit a complete account of efforts to settle this question. Several studies, however, deserve mention. Naeslund and Nylin[5] tagged red blood cells with radioactive phosphorus (P^{32}), injected them into the maternal circulation prior to delivery and later tested maternal and fetal bloods for radioactivity. They concluded that under certain circumstances transplacental transmission of erythrocytes can and does occur. On the other hand, the dissociation rate of phosphorus from red blood cells is so rapid that free phosphorus inevitably reaches maternal plasma and can cross the placental barrier as such, later to be picked up by the fetal erythrocyte. By 1951 Naeslund[6] employed Fe^{59} and performed seven experiments. In four of these the fetal blood cells showed considerable radioactivity, suggesting that some of the radioactive blood had crossed the placental barrier. All of Naeslund's subjects were delivered vaginally. Hedenstedt and Naeslund[7] injected elliptocytes into the circulations of three pregnant women

*Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 7 to 9, 1954.

and felt there was an increased permeability of the placenta to red blood cells. Martland and Martland[8] fortuitously were able to examine the blood of two pregnant women killed by carbon monoxide. Although they exhibited carboxyhemoglobin saturations of 48 and 88 per cent, respectively, the fetal blood (5 months and 9 months) contained none.

It is manifestly impossible to demonstrate the passage of fetal cells into the maternal circulation. On the other hand, it appeared to us to be technically feasible to attempt to demonstrate the reverse. If this could be done, we argued that passage from fetus to mother might be assumed. We decided to pursue this problem with the use of radioactive iron (Fe^{59}). The technical difficulties are considerably greater than with phosphorus, but, once incorporated, iron tends to remain in the cell during its life. Iron ingested or injected directly into the pregnant woman would find its way both into the cell and into the plasma. Therefore, it was necessary to employ donors in order to be able to inject washed tagged cells into pregnant women. Obviously these are not maternal erythrocytes although the assumption would have to be made that they would behave as such.

Subjects and Methods

One microcurie of Fe^{59} per kilogram of body weight was injected intravenously into group O medical student volunteers, and at least 10 days allowed to elapse before they were bled. The half life of Fe^{59} is 46.3 days. Twenty-five Rh-positive, normal pregnant women at or near term and 4 Rh-positive women in early pregnancy constituted the subjects of the radioactive part of our studies. They ranged in age from 15 to 40 years, with an average of 25 years. Of the 25 term women, 17 were delivered by cesarean section and 8 vaginally. In so far as possible, women about to be sectioned were selected as subjects in order to allow us to recover fetal blood from the cord, exposed by a small nick in the uterine wall, *before the uteroplacental junction was disturbed.* Four women in early pregnancy were aborted therapeutically by abdominal hysterotomy. Three operations were performed for hypertensive disease and one for early invasive cervical carcinoma. The entire fetus was available to us in three of these four instances.

Two hundred fifty milliliters of donor blood were withdrawn under sterile conditions. Clotting was prevented with anticoagulant acid citrate dextrose. The blood was centrifuged for 20 to 30 minutes at not more than 1,200 revolutions per minute to separate the cells, which were washed with saline, recentrifuged, washed, and resuspended in saline to restore the original volume. The pregnant women were thus transfused with tagged donor cells, from 13 minutes to nearly 10 days prior to delivery. The average elapsed time was nearly 26 hours, but in general we transfused the patient in the afternoon and delivered her the next morning.

Whole blood was collected both from the umbilical cord and from the parturient woman at the time of delivery. The fetal blood was heparinized to allow for an albumin flotation process for separation of erythrocytes from reticulocytes and leukocytes. The maternal blood was oxalated. Hematocrit determinations were done on each sample. The plasma was removed and analyzed for radioactivity.

Approximately 5 ml. of washed, packed red cells from each maternal sample were digested with concentrated sulfuric and 70 to 72 per cent perchloric acids. The infant samples were as large as possible, but seldom ex-

ceeded 8, and sometimes were as small as 2 or 3 ml. After digestion, the iron samples were electroplated on copper planchets following a technique described by Peacock and others.[9] This step is necessary for two reasons: the quantities of iron are too small to handle in other ways and the iron is plated in a thin film which is easy to count. A gas flow Geiger counter was used to determine the radioactivity of each sample, which was counted twice. A previously prepared Fe^{59} standard was counted with each group of samples to normalize the counts for decay and counter variations. In 21 instances the fetal reticulocytes were separated from erythrocytes by an albumin flotation process and were separately plated and examined for radioactivity. This was done in the belief that if Fe^{59} inadvertently had passed into fetal plasma, it would be taken up mostly by fetal reticulocytes. Fetal reticulocyte radioactivity, therefore, would be an index of the quantity of iron entering the maternal plasma by hemolysis and thence the fetal plasma. Details of these methods cannot be given here, but will be given in a monograph appearing elsewhere.

Results

Significant quantities of radioactivity were demonstrated in the erythrocytes recovered from the fetal blood or from the total fetuses of 25 of the 29 subjects of this study. The blood of four fetuses did not exhibit any significant radioactivity. Of the 25 term patients, the amount of tagged cells which could have crossed the placental barrier was represented by an average maternal whole blood volume of 4.4 ml. Unfortunately, the range of these determinations was large. The smallest amount of blood was 0.4 and the largest, 30.4 ml. Only four determinations exceeded 6 ml., however, and in one of these 232 hours elapsed between injection of the mother and delivery, giving ample time for cell breakdown and escape of tagged iron to maternal plasma.

TABLE I. TERM PREGNANCY. QUANTITY OF WHOLE MATERNAL BLOOD NECESSARY TO PROVIDE THE RADIOACTIVITY DEMONSTRATED IN FETAL BLOOD

INFANT WEIGHT (GRAMS)	DELIVERY, TYPE	TIME ELAPSED, INJECTION TO DELIVERY		MATERNAL BLOOD (ML.)
		HOURS	MINUTES	
2,250	CS	20	15	3.8
2,312	CS	17	15	2.8
2,319	CS	19	30	4.9
2,515	CS	18	0	0.4
2,545	CS	13	8	5.2
2,565	CS	15	0	1.4
2,690	Spont.	--	13	0.0
2,805	CS	14	59	0.8
2,825	CS	19	30	4.6
2,975	CS	13	40	0.0
2,975	Spont.	--	39	0.0
2,980	Spont.	--	30	6.5
3,055	CS	17	0	0.4
3,075	Spont.	44	18	1.5
3,085	CS	16	0	3.9
3,103	CS	16	30	30.4
3,170	CS	17	0	3.5
3,220	CS	20	20	0.8
3,280	Spont. SB	51	26	7.1
3,288	CS	19	0	16.1
3,331	CS	20	40	0.5
3,350	Spont.	1	15	0.7
3,515	Spont.	4	25	0.0
3,715	Spont.	15	0	0.7
3,884	CS	232	0	14.2

In 2 of the 4 patients whose fetuses exhibited no radioactivity the blood was given 13 and 39 minutes, respectively, before delivery. In so short a time, erythrocytes could hardly be expected to cross the placenta. On the other hand, in another patient who received blood 30 minutes before delivery, a relatively large amount of radioactivity (6.5 ml.) was found in the fetus.

In summary, in 4 women, no tagged cells appeared in the fetus, in 4 the amount represented more than 6 ml. of whole maternal blood, but in the remaining 17, the amount of whole blood varied from 0.4 to 5.2 ml. Table I summarizes these results.

In one of the therapeutic abortions, fetal blood only was collected. In the other three, the entire fetus was ashed. The results of these studies are shown in Table II.

TABLE II. EARLY PREGNANCY, THERAPEUTIC ABORTION (ABDOMINAL HYSTEROTOMY). QUANTITY OF WHOLE MATERNAL BLOOD NECESSARY TO PROVIDE THE RADIOACTIVITY DEMONSTRATED IN FETAL BLOOD

INFANT WEIGHT (GRAMS)	TIME ELAPSED, INJECTION TO DELIVERY		MATERNAL BLOOD (ML.)	
	HOURS	MINUTES	WHOLE FETUS	FETAL BLOOD
63	21	0	0.1	--
110	21	0	0.9	--
169	3	10	--	0.3
266	89	0	1.5	--

Separation of reticulocytes led us to no definite conclusions. Our results will, therefore, be reported in a monograph to appear later.

Comment

Obviously, among other experimental errors, two major problems concerning maternal erythrocytes containing tagged iron confronted us: hemolysis and termination of the natural life span. Moreover, all of this work is predicated upon retention of tagged iron in the circulating donor erythrocyte and absence of escape to maternal plasma. If Fe^{59} escaped from the cell into plasma it would readily cross the placental barrier and be taken up by the fetal erythrocyte. To avoid this error in so far as possible, we generally injected tagged, washed donor cells into the patient in the afternoon and delivered her the following morning. Few donor cells would reach the end of their natural life span during this period of time and, if hemolysis did occur, time for iron uptake into fetal erythrocytes would be reasonably short.

Although the work with Fe^{59} indicated that intact maternal blood cells crossed the placental barrier, the method was so cumbersome and vulnerable to error in so many of the separate processes that we were not satisfied. In fact, we almost abandoned the entire investigation as unsatisfactory because we could not be sure we had established even the fact of placental transmission of erythrocytes. The work of Hedenstedt and Naeslund[7] with elliptocytes kept recurring to mind and we cast about for some similar method of attack. Our hematologist assured us that introduction into a normal woman of blood from a patient with sickling trait would do no harm, and we decided to try it.

Studies With Sickle-Cell Anemia

Donors with the sickling trait, but without sickle-cell anemia, were secured through the courtesy of Dr. Helen Clark of the Department of Pathology, and cross-matched with pregnant recipients. As before, we selected women about to undergo cesarean section in order to secure fetal blood while the uteroplacental junction was intact. The maternal blood volume was calculated by the Evans dye method. Hemoglobin estimation and red-cell counts were made. Also the maternal blood was tested for sickling. None was present in any gravida of the series.

In the first study, 400 ml. of blood from a donor with sickling trait were injected into a 27-year-old white nulligravida at term. Cesarean section was performed 21 hours later. Blood was obtained from a small loop of funis, exposed through a nick in the uterus. About 50 smears of fetal blood were made and treated in three different ways to produce sickling: with sodium metabisulfite, with ascorbic acid, and by reduction of oxygen tension. Approximately 6 to 8 definitely sickled cells per slide developed in fresh, wet preparations. A long, involved calculation indicated that the erythrocytes in 0.0245 ml. of whole, maternal blood crossed the placental barrier in the 21 hours which elapsed between injection and recovery of fetal blood. It should be stressed that the donor blood contained no actual sickle cells. Therefore the donor cells presumably crossed the placental barrier as normally shaped erythrocytes and became sickled only when appropriate techniques were applied to the recovered fetal blood.

The second patient, a 33-year-old white multigravida, was transfused with 500 ml. of blood from another donor with sickling trait. Twenty-two hours later, the cord was exposed at laparotomy through a nick in the uterus, fetal blood was obtained for smears, and a 5 cm. section of cord was doubly ligated, removed, and fixed. The resulting anoxia produced sickling. In all, 129 sections of the cord were made. Cells thought to be sickled were found in 29, or 22.4 per cent, of the sections. They were also found in the wet smear preparations.

A third patient was injected with blood from a donor said to have sickling trait. Although the recovered fetal blood was treated as outlined and more than 350 smears were made, we were never able to find any sickle cells. We then returned to the donor, and blood taken directly from her could not be made to sickle by any known means. Apparently this donor did not possess the sickling trait. Therefore, this study serves as a control.

Finally, we secured a 5 cm. section of cord from the child of a normal white parturient immediately after delivery and using this as a control looked for sickle cells. None was found. On the other hand there were some artifacts, probably erythrocytes on edge, closely resembling sickle cells.

These studies indicate that normally shaped erythrocytes with a sickling trait crossed the placental barrier. This work needs confirmation, however. Nevertheless, the results so far seem to offer additional evidence that erythrocytes can cross the placental barrier, and, therefore, potentiate the rather oblique and cumbersome studies with Fe^{59}.

Summary

With the aid of washed donor erythrocytes tagged with Fe^{59} and injected into pregnant women, we were able to demonstrate significant amounts of radioactivity in the blood of their fetuses, in 25 of 29 subjects.

The average amount of radioactivity represented the tagged cells which would have been found in 4.4 ml. of whole maternal blood.

Two pregnant women at term were given blood from donors with sickling trait but without sickle-cell anemia. Sickle cells were thought to be demonstrated in the blood of the fetuses after appropriate technical treatment.

No sickle cells were seen in the blood or umbilical cord of two fetuses serving as controls.

We wish to thank the Department of Pathology and especially Drs. Helen Clark and E. E. Muirhead for their interest and help in the pursuance of the second part of this study.

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Discussion

DR. LOUIS M. HELLMAN, Brooklyn, N. Y.—Dr. Mengert has indicated that in all probability the infant in utero is "transfused" with maternal blood. For reasons he has clearly stated his experiments with radioactive tagged cells are suspect, but these suspicions certainly evaporate in the face of his sickle-cell evidence. Furthermore, these latter data confirm the previous experiments of Naeslund with elliptocytes.

Frankly, I am envious of Dr. Mengert's simple and apparently conclusive solution to this problem. Not only does it bear out the fact that currently stylish radioactive-isotope techniques may not yield as accurate results as more simple methods, but it seems to me to give a definitely affirmative answer to the question of placental permeability to human red cells.

There are two broad fields of questioning which occur to me, namely, the how and the why of this phenomenon. Is it purely a fortuitous circumstance that red cells should cross the placenta, or does it happen universally—and, if so, for what purpose? The latter might seem to be the case, for the infant appears well protected against the invasion of foreign red cells in that he never, or almost never, develops any reaction to them. The experiments with tagged red cells indicate that at least the iron, and probably the cells themselves, cross the placenta very early in pregnancy. While Dr. Mengert has said that these experiments are not conclusive, the inaccuracy is more probably concerned with the volume of blood crossing the placenta than with the fact that red cells do permeate this organ. It may be that this phenomenon has something to do with fetal nutrition—perhaps with the metabolism of iron or hemoglobin.

One would like to know more about the universality of red-cell transfer. As was stated, 4 of the 29 women in the isotope series did not demonstrate the passage of iron. Two were probably delivered too quickly. Nothing is said of the remaining 2, and one wonders if, here also, extraneous factors played a role in the prevention of transfer. As

far as the sickle-cell series is concerned, it seems to me to have been 100 per cent, for in the one case where transmission failed, the mother's cells could not be made to sickle by any "known means" and she therefore must be looked upon as a control.

The question of how this transfer occurs is another problem. Is it entirely due to the accidental breaking off of villi, leaving exposed fetal capillaries into which, almost by accident, fall maternal cells; or do these red cells traverse the placental barrier? There is good evidence that villi do break off, although this occurrence is probably more frequent late than in early pregnancy. Whether maternal cells can then enter the fetal capillaries depends on two factors, namely, the size of the capillaries and the differential in pressure between the two systems. The capillaries in the small terminal villi are very tiny, varying from 5 to 20 microns in diameter in a fixed specimen. Of course, the break might occur in the larger stem villi. As to the pressure differential, little is known in regard to this factor, as it concerns either the intervillous space or the fetal capillaries. Surely the pressure cannot be less than the venous pressure of the host. From current data the venous pressure in the umbilical cord approximates that of the maternal venous pressure. Certainly the differential is not great enough to account for a transfusion of from 4 to 6 c.c. of maternal blood per day. Furthermore, if this volume continues for the last two months of pregnancy, the infant must necessarily have a complete exchange transfusion.

Apparently villi in actual fact are not as they seem under the conventional light microscope. When viewed under the electron microscope, they show many projecting photoplasmic microvilli. The electron microscope not only invalidates the tenets of the Grosser classification of placenta by layers, but shows the syncytiotrophoblast as a dynamic rather than a static barrier, in which pseudopods of cytoplasm flow out, close in again and engulf droplets of plasma or even maternal red cells, and perhaps transfer them to the fetal stream by a process of planocytosis. This method of transfer would be more in keeping with a daily volume of 10 million red cells, as calculated by the essayist.

Dr. Mengert and his colleagues have proved, at least to my satisfaction, the occurrence of red-cell transmission. I am sure they have speculated far more ably than I on the "why's" and "how's" of this situation, and I would be delighted to hear some comment on these aspects.

DR. CURTIS J. LUND, Rochester, N. Y.—I do not suppose anyone seriously doubts that fetal erythrocytes can and do cross the placental barrier. The proximity of the two circulations in the hemochorial placenta of the human being makes interchange rather simple in the presence of small defects. Isoimmunization has been described in animals with more complex placentation, however, such as the mare and the sow. Although the antigenic material, presumably the maternal erythrocyte, is able to cross this difficult placental barrier, the specific antibodies are unable to recross the placenta, so that the foal or the pig does not have difficulty until the antibodies are ingested through the colostrum. Dr. Mengert has shown clearly and convincingly from the transfusion studies of blood with the sickling trait that minute amounts of maternal blood can cross the placental membrane. The tracer studies are less convincing, and yet they point clearly to the same conclusion. Our own experiences with the transmission of soluble substances showed that there is great individual variation. Such variation might account for the scattered results, although the technique is obviously a difficult one and subject to considerable variation.

I am not certain that it is impossible to demonstrate the passage of fetal cells into maternal circulation. In a very recent paper, Chown states that he was able, by agglutination techniques, to demonstrate cross-transfusion of the mother during the last three weeks of pregnancy. In one patient he estimated that 5 to 10 per cent of the maternal cells were fetal in origin and that the baby had lost between 160 and 300 ml. of whole blood. The baby, incidentally, was anemic at birth. It is obvious that such occurrences are rare.

Certainly these modern research techniques have demonstrated the vulnerability of the placental circulation. One must assume, however, that the direction of flow, whether

from mother to fetus or from fetus to mother, depends upon the differential of blood pressure between the two systems: If one or the other were consistently elevated, then the direction of flow would be clearly established. On the other hand, if the pressures of both systems are approximately equal, then some mixing would occur and temporary shunts might be expected in one direction or the other.

DR. MENGERT (Closing).—Dr. Hellman's speculations on the "why" and the "how" of placental transmission are so much more advanced and detailed than ours that I will not attempt to comment on them.

I will close by saying that this has been a very long and tedious study. We are inclined to think that the red blood cell does cross the placental barrier. We are still working, but this time we are continuing our work with the sickle-cell preparations.

LIMITED INFLUENCE OF DIETHYLSTILBESTROL ON LACTATION*†

H. Close Hesseltine, M.D., Jorge Bustamante, M.D., and
Cornelius A. Navori, M.D., Chicago, Ill.

(From the Department of Obstetrics and Gynecology, The University of Chicago and The Chicago Lying-in Hospital)

A CONSIDERABLE portion of the animal kingdom belongs to the group known as mammals. Many dissimilarities of mammals exist. Size varies greatly from the small species like the mouse to the largest of all animals, the whale. Dietary patterns run the gamut of herbivorous, carnivorous, and omnivorous. The habitates vary equally as much. The one common factor of mammals is breast feeding. Although mammary function serves a necessary role in the rearing of the young, comparatively little has been discovered on the exact nature of lactation. In proportion to the importance of the perpetuation of the race there has been inadequate research and study of the human mammary gland.

Even today breast feeding is the preferred method of starting the human baby. Too often, however, breast feeding must be supplemented or totally replaced. Theoretical reasons for this inadequacy are many, but established proof is less clear.

There are times when it would be desirable to prevent the onset of lactation or to discontinue lactation quickly without engorgement and distress. It is generally believed that diethylstilbestrol will delay or prevent the onset of lactation in women. The fact that distressing engorgement of the mammary glands does occur quite often after the discontinuance of this estrogen has not resulted in a general consideration of the action of diethylstilbestrol upon the breast tissue and the course of events. Even though there was documented evidence of breast function in relation to this estrogen, it was felt that concentrated observation on inhibition of lactation would be of teaching value. Perhaps observation on alteration of uterine involution, late postpartum uterine bleeding, and the nature of lactation might merit a pilot study.

Review

Estrogens when administered antenatally (1) did not affect the labor, (2) did not cause delayed onset of lactation, but (3) did induce often copious lactation, so claimed Robinson.[9] Control studies showed evidence of a higher percentage of deficient lactation in those who did not receive an estrogen, especially when there were complications during the course of labor. Thus she concluded that it was not so much the estrogens which delayed the onset of lactation, but factors related to difficult labor.

*Supported in part by the Fiftieth Anniversary Puerperal Sepsis Fund.

†Presented at the Sixty-fifth Annual Meeting of the American Association of Obstetricians and Gynecologists, Hot Springs, Virginia, September 9 to 11, 1954.

It is common knowledge that lactation is heralded by the engorgement between the second and fourth postpartum days. Numerous reports have shown that this initial engorgement could be prevented or minimized by the use of estrogens. Such observations supported theories of endocrinic control of the physiologic behavior of the mammary gland.

As early as 1936, Nelson[8] propounded this theory of estrogenic inhibition. His explanation was based on the premise that the high estrogenic level in pregnancy prevented lactation, and with the rapid withdrawal of estrogenic substances subsequent to delivery lactation started. The inhibiting action of estrogen on lactation aroused some doubts; with others, Abarbanel and Goodfriend[1] hold that the beneficial results following the administration of estrogen to lactating women are due rather to relief of painful engorgement (this condition is being ascribed to lymphatic and venous stasis) than to inhibition of milk secretion.

Well-supported but unusual experiments revealed that estrogens may function both as lactogenic and galactopoietic agents (Folley[4]). Folley and associates[6] applied diethylstilbestrol locally and proved the galactopoietic effects on ruminants. They applied 1 per cent diethylstilbestrol dipropionate ointment three times weekly to the udder of a virgin female goat and "daily milking began." They experienced the following: there was a latent period of 30 days during which a few milliliters of fluid were secreted daily, after this the milk secretion suddenly increased to a maximum of 1,500 ml. daily and then a slow decline occurred. They obtained similar results with two other virgin goats as well as with a virgin heifer. The milk secreted by this artificial induction was normal in composition and "indeed was of excellent quality." The control for this experiment consisted of the same milking and application of the base ointment (estrogen free). Although the colostral state was noted, lactation was not induced. Thus milk could not be obtained from either a goat or a heifer by milking and by inunction with an estrogen-free base ointment.

Walker and Stanley[10] used a 34-month-old virgin Jersey heifer for their experiment to increase milk production after lactation had come on by biologic process. The animal was given a total of 50 mg. stilbestrol dipropionate intramuscularly in 5 mg. doses. The udder showed a marked increase in size. With subsequent discontinuance of stilbestrol dipropionate the milk yield increased within a 12 day period to a maximum of 5,320 c.c. In 8 months' time 2,880 pounds of milk was produced. It yielded an average of 7 per cent of butter fat.

The mechanism of these lactogenic and galactopoientic effects seems most probably mediated by the anterior pituitary, which is believed to release the lactogenic and galactopoietic hormone complexes in response to the stimulus of estrogen or perhaps to metabolic derivates thereof. Folley[5] has suggested that the estrogen threshold for pituitary stimulation is probably lower than for inhibition, so that the factor determining whether stimulation or inhibition shall prevail would be the level of estrogen in the body fluids. Other

authors believe that the action of estrogens is probably mediated through the ovaries, since moderate doses of estrogens have no effect in castrated animals.

Yet Malpress[7] demonstrated that estrogenic concentration and the metabolism of the given estrogen are of paramount importance for the fulfillment of this physiologic process.

The theoretical background of hormonal mechanism may not be fully understood. Empirical studies by Barnes[2] support the widely claimed beneficial effects of symptomatic relief of engorgement without interference with lactation. Hence its usefulness in suppression of milk secretion in breast-feeding women seemed proved.

A number of schedules of administration of the hormone have been suggested. It appears to be the general belief that the dosages fall primarily into two patterns. One is the small amount with each breast feeding. For example, 5 mg. of stilbestrol given with breast feeding should relieve pain and tightness of the mammary glands and enhance favorable lactation. Another and equally popular schedule for milk suppression is the single total daily amount, which may be as low as 5 to 10 mg. of diethylstilbestrol.

The lack of agreement is evident by the fact that the amount of stilbestrol used in various studies to inhibit lactation ranged from a daily total of 5 to 1,000 mg., as quoted by Abarbanel and Goodfriend,[1] Connally, Dann, Reese, and Douglass,[3] and Barnes.[2] A full review of the world literature on this subject would be disproportionate in this paper. Most random reviews of the communications would reveal the lack of uniformity of authors' views on acceptance and recommendation of stilbestrol for either the stimulation of breast feeding or the suppression of lactation.

Material

The patients for this series consisted principally of service patients, all white. Private patients, although fewer in number, were included in the study. One hundred fifty-three patients received 5 mg. or 25 mg. diethylstilbestrol daily from four to ten days post partum, starting the second day of the puerperium. The group consisted of 27 primiparas and 126 multiparas, all of whom had an uncomplicated labor and delivery and a normal puerperium. All patients who encountered complications or needed special therapies were deleted from the study. An even number of 70 of the patients lactated, while 83 chose not to nurse the baby or were advised against breast feeding on a medical basis.

Table I designates the number in each category as related to stilbestrol dosage and to the lactational state. Initially 5 mg. was given once daily beginning on the second postpartum day, and the patient was maintained on this daily amount for 5 days until 40 patients had been observed. One half of this number (20) were able to lactate adequately. The other 20 nonlactating puerperal women responded in the expected manner, avoiding the distress of engorgement for 7 to 8 days.

The second step consists of 31 lactating and 4 nonlactating women (total of 35) maintained on the same dosage for 10 days. These numbers are unbalanced because at this time there were only these relatively few who did not lactate. After these 75 patients were treated for 5 to 10 days, another group was given 25 mg. diethylstilbestrol once daily beginning on the second

postpartum day for 4 days and later extended up to a maximum of 8 days. The total dosage of this estrogen varied from 25 to 200 mg. A total of 78 individuals received the larger daily dosage.

TABLE I. PATIENTS RECEIVING STILBESTROL (5 AND 25 MG. DAILY)

DOSE					
DAILY (MG.)	TOTAL (MG.)	DAYS	LACTATING	NONLACTATING	TOTAL
5	25	5	20	20	40
5	50	10	31	4	35
25	100	4	1	12	13
25	125	5	12	28	40
25	150	6	6	9	15
25	175	7	0	5	5
25	200	8	0	5	5
			70	83	153

The 70 lactating women used the customary breast garments. Meanwhile only 13 of the 83 nonlactating wore breast supports.

TABLE II. THE EXTENT OF MAMMARY ENGORGEMENT DURING THE HOSPITALIZATION (PER CENT)

	MINIMAL	MODERATE	MAXIMAL
Lactating	28.5	64.3	7.1
Nonlactating	33.7	59.0	7.2

Results

Subjectively, nearly all of the patients believed in the comforting results of the therapy. As a rule, these patients either did not have the distress of engorgement or would not admit it. Subjectively, the lactating women believed that they had satisfactory nursing performance for themselves and their babies. In this small series there were no special problems of a deficiency in the amount of milk as judged by the weight course of the infants.

Efforts to evaluate the mammary-gland response by circumference measurement was unsatisfactory, for the changes were not properly significant and changes in the thoracic cage due to respiration further confused the situation.

Finally, for lack of any dependable measurement of objective interpretation, palpation was used. Three degrees of engorgement were selected; minimal (or no filling), moderate (or partial filling), and maximal (or complete engorgement). It will be noted (Table II) that one-third or less did not show mammary filling of any appreciable amount, yet the lactating women fed their babies adequately.

Moderate response occurred in 64 per cent of the lactating and 59 per cent of the nonlactating women. Only 7 per cent of each group had partial or full engorgement.

It was not possible to ascertain what number of the nonlactating group had engorgement after leaving the hospital. Not one of the 153 returned to the hospital because of profuse bleeding or hemorrhage.

The 7 per cent in the lactating group represents 5 patients while the same per cent in the nonlactating represents 6 individuals. All 11 encountered the engorgement sometime between the third and the eighth postpartum days. There is no evident significance of the dosage or any other factor.

Most patients did not use breast binders, yet the physiologic process of regression of the gland substances seemed normal. Furthermore, these patients did not complain of discomfort due to the absence of supporting measures.

All of these 153 remained free from breast infections.

Lactating women did not report any untoward effects on milk production after their discharge from the hospital. There was no clear-cut evidence of any significant increase in milk production among either the primiparas or the multiparas while under observation.

The drug tolerance was good. Nausea did not occur in any. A few patients were started on this regime but were removed from the series because of unrelated complications or because of need for other medications.

Summary and Conclusions

One hundred fifty-three patients, 27 primiparas and 126 multiparas, received 5 to 25 mg. diethylstilbestrol daily for four to ten days post partum.

The 70 lactating and 83 nonlactating women exhibited almost identical response to the drug. Minimal response occurred in nearly one-third; moderate response was present in slightly less than two-thirds; and full maximal response or engorgement occurred in approximately 7 per cent of both groups.

The fact that 13 of the 83 nonlactating women needed breast binders indicates that diethylstilbestrol did not totally alleviate discomfort or lactopoiesis.

The fact that 70 women supplied sufficient nourishment for their infants even though they were receiving diethylstilbestrol in amounts that were supposed to inhibit or prevent lactation indicates that other factors are concerned with the onset and maintenance of lactation or its prevention.

It could be concluded that 90 per cent or more of the lactating women avoided the primary engorgement of the breasts by the use of estrogens. This is in accord with a number of reports. The percentage of nonnursing women that will have engorgement after discontinuance of diethylstilbestrol could not be accurately determined.

Accordingly, it appears that diethylstilbestrol is not a drug to use to reduce the milk supply nor will it prevent the establishment of lactation where nursing is permitted. Diethylstilbestrol as used in this limited group was not followed by complications of subinvolution or delayed puerperal hemorrhage.

Notwithstanding these data, diethylstilbestrol seems to have a place in reducing the incidence of primary breast engorgement, but the reason was not determined. The reliability of this virtue in any one patient, however, is unpredictable.

Thus the justification and indication for the use of diethylstilbestrol should be on an individual basis. Moreover, breast engorgement following withdrawal of the diethylstilbestrol may be as distressing as without its use. These patients are usually at home and thus must endure a day or so of painfully engorged breasts without the aid of proper analgesics.

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Discussion

DR. BERNARD J. HANLEY, Los Angels, Calif.—The essayist has reported some interesting animal experiments in which stilbestrol appeared to have both a lactogenic and a galactopoetic effect. Then he reported a series of 153 nursing and nonnursing mothers who were given oral doses of stilbestrol, varying from 5 to 25 mg. daily, in which the results were almost opposite to those obtained in the experimental animals. This paradox is understandable when one considers the numerous conditions in which stilbestrol has been alleged to produce good therapeutic results. His title, "Limited Influence of Diethylstilbestrol on Lactation," coincides with the observations most of us have made on its use in this condition. I believe the explanation lies in the varying degrees of response that the breast tissues of different individuals make to ovarian hormones, especially estrogen.

Those of us who have practiced twenty years remember how unsatisfactory was the treatment of engorged breasts in the nonnursing mother before the advent of stilbestrol. It was only natural that we should turn to this medication when reports of its efficacy were first published. In 1942 I reported on its use, also in 153 patients, who for one reason or another did not wish to nurse. These patients were given 2 mg. of stilbestrol orally, morning and night, for five consecutive days, starting the day after delivery. All other routine postpartum orders were the same for both the nursing and the nonnursing mothers. I felt then, as I feel now, that stilbestrol did not prevent the secretion of milk, as Hesseltine has emphasized, but that it did alleviate a great deal of the pain associated with breast engorgement, thereby bringing relief to the patient. It is not clear in my mind just how this effect is brought about, but I am reasonably sure that the drug does no harm. I have used this small dosage of stilbestrol in more than 2,000 private cases of nonnursing mothers, and while its action was somewhat limited, all in all the results were fairly good. Occasionally a patient developed breast engorgement after she went home from the hospital and required a second course of medication; there were also a few cases of withdrawal bleeding, but all of these responded to bed rest and ergonovine and none required hospitalization. I continued the use of stilbestrol until 1953, at which time, encouraged by the report of Dr. Dodek, I started using Depo-Testosterone. So far the results have been fairly satisfactory, although an occasional patient still has painful breast engorgement and requires some stilbestrol.

DR. J. ROBERT WILLSON, Philadelphia, Pa.—Dr. Hesseltine's interesting study on the administration of stilbestrol to puerperal women has demonstrated again the fact that this drug has little effect upon the secretion of milk, and suggests that the mechanism responsible for lactation is considerably more complicated than it appears to be. Although it is apparent that breast engorgement is caused primarily by vascular and lymphatic congestion rather than by the sudden appearance of milk in the acini and ducts, the reason for the phenomenon itself and for its prevention by estrogen or by testosterone is not obvious. It seems certain from the results of aniaml experimentation and from the observation of recently delivered women that the mechanical stimulus of milking or suckling is at least as important in initiating and maintainng lactation as is the proper hormonal preparation of the breast structures.

Engorgement in both nonnursing and nursing women produces transient symptoms which ordinarily do not last longer than 48 hours and which can readily be controlled by the application of ice and by the administration of aspirin and codeine. I stopped using endocrine preparations to suppress engorgement several years ago, because in a high percentage of patients treated with either stilbestrol or the male hormone the breasts became engorged after the patients had gone home, where it was far more difficult to control the symptoms. Like Dr. Hesseltine I am not aware of increased bleeding caused by the

stimulation of stilbestrol. The results of this study, however, suggest that the use of estrogens to prevent engorgement might be beneficial if the mother is nursing her infant. If the breast is soft rather than tense, distended, and painful, the nipple can be more easily grasped by the infant and he might well learn to nurse earlier and, in addition, might obtain a more adequate amount of milk during the first two or three days after lactation is initiated. If the infant does obtain more nourishment and begins to gain sooner, he might not be changed to a bottle as promptly as many now are. In those who are not nursing I can use no reason to use any type of endocrine preparation. Endocrines also are contraindicated when the infant finally is weaned after several weeks of nursing, because true engorgement occurs only within the first few days after delivery and the discomfort at weaning time is due to filling of the breasts with milk.

The widespread dissemination of the results of this study should aid in correcting the inadequacies in information and the inaccuracies in terminology regarding the control of the symptoms accompanying lactation. Stilbestrol may prevent "engorgement" of the breast, but it seems to have little effect upon "lactation" or the actual production of milk. I am sure that many individuals have been prescribing estrogens unnecessarily and ineffectively in an attempt to "suppress lactation," which is virtually impossible.

DR. HESSELTINE (Closing).—Dr. Hanley and Dr. Willson could properly have challenged our conclusions and criticized the lack of balance among the cases. Had we known the final details, we would have tried to obtain a larger series.

Department of Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Review of New Books*

Out of Wedlock: A Study of the Problem of the Unmarried Mother and Her Child. By Leontine Young. 261 pages. New York, 1954, McGraw-Hill Book Company. $4.00.

Dealing with a little-understood problem, this book is timely for with the upsurge of juvenile delinquency one may expect an increase in the number of babies born out of wedlock. Undoubtedly the problems and etiological factors connected with juvenile delinquency are in the majority of instances applicable to the subject discussed in this book.

The author very nicely develops the theme that these out-of-wedlock pregnancies are no accident but rather that in most instances they are intentional. This may be surprising to most people but one must acknowledge the wide experience of the author and consider the evidence with an unbiased mind. It is enlightening to learn that most of these mothers are psychologically ill and need help, not condemnation. The book does not condone pregnancies conceived out of wedlock but rather tries to point out the reasons for them and the procedures that should be followed to help correct the problem.

The plea for a more intelligent and enlightened attitude toward the baby in these situations is refreshing and it is to be hoped that it will find enthusiastic reception by the workers involved in this phase of social work. The cost to society, not only in money, but in developing abnormal personalities because of an improper attitude, is tremendous.

This book should find a wide reception and provoke more thought about a problem that is ever present.

The reviewer recommends this work for all who may be called upon to handle these women.

Beyond the Germ Theory. By Iago Gladston, Editor, Health Education Council. 182 pages. New York, 1954. Published by Health Education Council. $4.00.

This book is written by several authors each of whom is an authority on a phase of the subject under consideration. This subject is the effect of deprivation and stress, not only upon the individual, but also on the entire society. That deprivation and stress do produce profound effects even to the point of invalidism of the body as well as the mind is undeniable. It is probably not generally appreciated, however, how destructive these two states may be. The author attempts to open our eyes to their seriousness and to emphasize the need for recognizing that many organic disturbances may be the end result.

Many examples are cited to prove this theme but there will be some disagreement with and critical questioning of one experiment. The conclusions drawn from the experiment of removing mothers from their babies early in the first year should be questioned. There are too many unexplained factors to conclude that all of the disturbances were due to the deprivation of one important emotional factor.

The last two chapters are the most thought provoking for they touch upon the current weaknesses in our society. Apathy apparently is becoming more prevalent and affecting the attitude of society toward more than one phase of our life. The danger of this is rightly emphasized.

*The Advisory Committee on Policy has agreed that most book reviews need not be signed.

Menorrhalgia: Menstrual Distress. By William Bickers, Springfield, Ill., 1954, Charles C Thomas. 97 pages, with 11 illustrations. $2.75.

This monograph concerns itself with a discussion of premenstrual tension, dysmenorrhea, and pelvic vascular congestion, grouped under the term "menorrhalgia."

Dr. Bickers devotes a considerable portion of his book to a discussion of the physiology, pathology, and etiology of this common and often perplexing syndrome. This section of the monograph is detailed and complete. Indeed, it seems that the author devotes too much space to the various conflicting theories concerning this syndrome.

The chapters relating to the clinical picture of this disease and its treatment are easily understood and explicit. It is regrettable, however, that Dr. Bickers did not develop this portion of the monograph more completely.

New Concepts of the Causes and Treatment of Diabetes Mellitus. Proceedings of Symposium, National Vitamin Foundation, New York. 181 pages. 1954. $2.50.

This book is a report of the proceedings of the symposium on diabetes which was sponsored by the New York Diabetic Association in October, 1953.

Presentations were made by thirteen essayists, each an authority in the specific field.

A special presentation by Professor B. A. Houssay was entitled "Some Hormone Interrelationships in Experimental Diabetes." He reported that his pupils have shown that female sex hormones have a tendency to decrease the incidence of induced diabetes in experimental animals, while androgens tend to do just the opposite. Other steroids had no effect. Estrogens appear to cause a hypertrophy of the islets of the pancreas (B cells). These hormones have been used to treat animals having alloxan diabetes. One-half of the animals with mild diabetes were cured by estrogen administration.

The following list of titles of papers presented shows the diverse fields covered:

"The Hereditary Obese-Hyperglycemic Syndrome in the Mouse"
"Lipogenesis in Experimental Diabetes"
"The Endocrine Regulation of Carbohydrate Metabolism"
"Some Hormone Interrelationships in Experimental Diabetes"
"The Action of Insulin"
"The Hyperglycemic Glycogenolytic Factor of Pancreas"
"Control of the Complications of Diabetes"
"Disturbances in the Metabolism of Vitamin B_{12} in Diabetes and Their Significance"
"Indications for the Use of Various Insulins"
"The Management of Diabetes During Pregnancy"
"The Effects of Life Situations and Emotions Upon the Management of Diabetes"
"The Management of Surgical Infections in Diabetes With Special Reference to Streptokinase-Streptodornase"
"The Nutritional Management of Diabetes"

Presentations vary in their medical value and completeness. The section on "Management of Diabetes During Pregnancy" is far from adequate: It merely reports the results with 140 diabetic pregnancies over a period of 18 years at the Boston Lying-in Hospital. There was a 23 per cent perinatal mortality. One-seventh of the patients were delivered by cesarean section.

The publication, while not a perfect one, is of value to the physician whose primary interest is along lines other than diabetes.

Reproduction and Sex. By G. I. M. Swyer. 280 pages. London, 1954, Routledge and Kegan Paul, Ltd. 25s.

This fine book is the second in a series being published by Routledge and Kegan Paul, Ltd., of London under the general title, "Survey of Human Biology." The books are written for everyone interested in the health and welfare of human beings. They are also meant to be of service to students and specialists in the various fields of biological science. Thus, one purpose of this series of books is to convey factual information. The other purpose is to develop the relationship between the facts and the underlying social and economic problems in the world of today. *Reproduction and Sex* is 280 pages in length and it is written in concise, uncomplicated language. It contains clear illustrations, a well-selected bibliography, and a fairly complete glossary. The first four-fifths of its pages are concerned with human reproduction and the last one-fifth is concerned with sex.

The explanation of reproduction in the male and in the female is done exceedingly well. In spite of the numerous but necessary scientific details, the description of reproduction is simple and understandable. Furthermore, it succeeds in integrating fragments of genetics, embryology, physiology, anatomy, and histology into a clear and composite picture. This is followed by a brief account of some of the common complications of pregnancy and labor.

Not until he deals with infertility and contraception, does the author become concerned with the relationship between facts and social and economic conditions. For instance, he states, "Nowadays, the majority do not wish to have children during the first few years of their marriage, mainly for economic reasons and because of housing difficulties." This bare statement of fact has profound implications for the Western Society of today. Both chapters on infertility are very well done with the exception of two facts. The first is the statement, "there is not the slightest doubt that the commonest of the causes of infertility in the female is some defect in the cervical secretion, etc." This claim is not supported by scientific evidence. The second fact is one of omission, wherein the author fails to state that among the causes of sterility in women is endometriosis.

It is in the shorter part of the book, the part devoted to sex, that the author is better able to combine information with related social problems. After dealing briefly with the Freudian concept of sexual development, he proceeds directly into the Kinsey reports, from which he quotes extensively. In regard to the male, the most significant fact brought out is the great misconception about homosexuality. The author states, "The fact that the extent of the practice is so great, in face of its strong condemnation by organized social opinion and vicious repression by the law, nevertheless strongly suggests that in the absence of these restraints, many more individuals would be involved." Another important fact concerns the great difference between male and female in the development of maximum sexual drive. Whereas the female does not reach the peak of sexual urge before the age of twenty-five or thirty, the male does so when he attains to puberty. Unfortunately, the importance of this physiologic disparity is not discussed. For example, New Zealand is in great turmoil over organized immorality among children in their early teens, as well as some who are only 12 years of age. After mentioning the more common sexual deviations, the author concludes this excellent book with two refreshing sentences, "Not until there is a better balanced, healthier outlook on sex by the general public, can it be expected that a rational attitude, free from vindictiveness, will be shown by the law. By then, however, it is likely that sexual offences would themselves have become far less frequent."

Holt's Pediatrics. By L. Emmet Holt, Jr., and Rustin McIntosh. Twelfth edition. 1485 pages with 272 figures. New York, 1953, Appleton-Century-Crofts, Inc. $15.00.

"This volume represents the Twelfth Edition of Holt's *Diseases of Infancy and Childhood,* originally written in 1896 by the late L. Emmet Holt."

This excerpt from the title page reflects the reputation and consistent value of a work well done. The present edition, the twelfth, does not detract from the reputation established by its predecessors. In fact, it must enhance the title.

The list of contributors is a "Who's Who in Pediatrics" with asides into related fields. For example, Dr. George W. Thorn writes the section on "The Adrenals," Dr. Mark Ravitch contributed the section on "The Intestines," and Dr. Frank Ford the section on "The Nervous System."

All sections are not of equal standing, as is to be expected in a volume of such size and with so many contributors. Also, the time required to assemble the material tends to make some sections out of date. For example, the discussion on retrolental fibroplasia is scarcely up to date either in context or references, the latest reference being 1950. On the other hand, the sections on growth and development and nutrition are most complete with up-to-date references.

The editors are to be congratulated upon the compiling of such a uniformly well-written and complete text. Almost all sections are clearly and concisely written and are a credit to the specific authors. This wealth of talent and information may be recommended as a text.

Health Services for the Child. By Edward R. Schlesinger, Associate Director of Medical Services, New York State Department of Health. 403 pages. New York, 1953, McGraw-Hill Book Company. $7.50.

This is a summary of current maternal and child health services available in this country. It is written primarily for the family physician by a pediatrician trained in public health and experienced in the administration of the Maternal and Child Health Services of the New York State Health Department.

The book is subdivided into four parts dealing with basic considerations, essential health services, health supervision, and special problems. The section on basic considerations summarizes the important elements in the formulation, planning, and implementation of a community maternal and child health program. There is reference to selected historical and statistical background data, to the role of the physician, public health nurse, and medical social worker, and to hospitalization.

The section on essential health services considers six basic aspects, viz., health appraisal of the growth and development of the child, promotion of mental health, control of communicable diseases, dental health, nutrition, and accident control.

These and other aspects are then reconsidered in relation to the health supervision of the mother during the prenatal period, and of the newborn child during successive stages from the neonatal period through adolescence.

The last section is a short review of some of the services available for children with physical, emotional, and social handicaps. The brief comments on intellectual, emotional, and social handicaps in the final chapter appear to be disproportionate to current interest and activity in these fields.

The book should be useful to the general practitioner who is so burdened by the immediate demands for the treatment of the sick that he may have been out of touch with developments in disease prevention and in the promotion of maternal and child health. It should also be valuable to residents in pediatrics and obstetrics and to public health students as a summary of good maternal and child health practice in the United States. On the other hand, it may be of more limited use to the obstetrician and pediatrician who have pioneered in health promotion and are daily engaged in its practical application.

The Mechanism of Labour. By Erik Rydberg. 180 pages with 37 illustrations. Springfield, Ill., 1954, Charles C Thomas. $4.75.

Dr. Rydberg is one of the world authorities on the problem of the study of the mechanism of labor. His recent article appeared in the July issue of the AMERICAN

JOURNAL OF OBSTETRICS AND GYNECOLOGY. This present monograph explains in lengthy and meticulous detail his theory of the mechanism of labor in the normal patient with a vertex presentation.

To study this problem he first thoroughly reviews both the historical and current opinions on the subject, then attempts to duplicate the actual birth of a fetal head experimentally. He has studied fetal passage roentgenologically and cinematographically and has concluded that vertex rotations and flexions are determined by head configuration alone.

The author duplicates the pelvis with a lubricated rubber tube and simulates the fetal head with a carefully shaped wooden figure. Then he passes the head through the tube under air or manual pressure and observes the model's transitory movements.

This experiment supposedly duplicates the mechanism in vivo. Since the movements vary with cephalic configuration he proves, at least to his own satisfaction, that the mechanisms of normal labor are determined solely by head shape.

Dr. Rydberg divides his book into several chapters, covering theory, history, and experiments. The clinician, however, may fully grasp the important points of the monograph from the summary in the seventh chapter.

Practical Obstetrics. By Bruce T. Mayes. 500 pages with 177 illustrations. London, 1954, Angus and Robertson. 87 shillings and sixpence.

This is an exciting book! It begins dramatically with a death and the imagination of the reader is held as the author proceeds to describe how the patient died from preeclamptic toxemia. The subject is then discussed with emphasis on prevention and treatment, and thus he establishes a pattern for the various subjects discussed throughout the remainder of the book.

The first edition was evolved from a series of bulletins on obstetrical subjects which were written for graduates serving in the armed forces during World War II. The second is an expanded version resulting from the success of the first edition, and from the great value of the original bulletins. The book is primarily intended for the general practitioner, but the specialist will gain much practical and useful information from these graphic pages. The author is obviously a first-class teacher, and the way in which he presents the various subjects gives the reader a clear picture of his teaching methods.

The approach is essentially conservative, and the witty aphorisms, sprinkled as if with a pepper pot throughout the whole book, help to drive home salient points.

Professor Mayes has chosen those subjects which the busy private practitioner is most likely to encounter, and in addition there are chapters on sterilization, sterility, and infertility. It is felt, however, that without greatly enlarging the book, chapters on transverse presentation and pyelitis could have been introduced with some advantage, and that even appendicitis and tumors of the ovary and uterus might be considered for a later edition. Certain dogmatic statements, such as "no serious attempt has been made to relieve vulvar varicosities," may cause some disagreement.

Notwithstanding these minor criticisms, this is an excellent book and its popularity is sure to increase as it becomes more widely known. The illustrations and the general setup make this an attractive purchase for the potential reader of a book on practical obstetrics. Eighty-seven shillings and sixpence (approximately thirteen dollars), seems expensive for a book of this size, but the price may be accounted for by the excellence of the numerous drawings, many of which are in color.

Having a Baby. By J. F. Robinson. 92 pages with 23 illustrations. London, 1954, E. & S. Livingstone. $2.50.

Consisting of some ninety pages, this little book for those who are about to be married is full of information concerning anatomy in relation to childbirth, the menstrual cycle, contraception, sterility, the beginning of pregnancy and antenatal care, exercises during pregnancy, relaxation during pregnancy and labor, growth and development of a baby, twilight sleep and analgesia in labor, lying-in, and feeding the baby.

It would seem an immense task to condense all this into a small book. The author has accomplished it very successfully in an easy, lucid style, abounding with common sense. To those contemplating parenthood, this book will give reassurance and up-to-date information in a most interesting form, accompanied by illustrations remarkably simple and easy to understand. Although the book was intended for use in Great Britain, the few references to local conditions will not detract from its value to those in other countries.

Primer of Pulmonary Function. By Harold Guyon Trimble and James Kieran. 22 pages. Oakland, Calif., 1954, California Health and Tuberculosis Association.

This is an introduction to the subject of pulmonary function, written simply, with readily applicable examples. It discusses and explains the various tests of pulmonary function in a practical manner.

A very useful table of lung volumes and formulas is reproduced, and a graph of lung volume subdivisions from Pappenheimer (J. Federation Proc., 1950). This collection of data, together with its information on the cost of equipment, will prove to be most useful for the general practitioner and medical student and those wishing to be briefly acquainted with newer methods in this field.

Problemi dello Stroma Endometriale nelle Metropatie "disfunzionali," a Contegno Emorragico ed anemorragico (The Problem of the Stroma of the Endometrium in Dysfunctional Bleeding, both Hemorrhagic and Nonhemorrhagic). By F. Destro. 28 pages with 14 illustrations. Fidenza, 1953, Tipografia Tito Mattioli.

The author describes the problem of the "silver wire reticulum" and of the "stromal mucoid" of the endometrium in cases of dysfunctional metropathia, both hemorrhagic and nonhemorrhagic, comparing it with the particular modification of the normal menstrual cycle, and of other pathological conditions of hormonal dysfunction.

He finally interprets the genetic mechanism and meaning, in the light of modern knowledge on the constitution and function of the connective tissues.

L'endometriosi (Endometriosis). By F. Destro, M. Goisis, and C. Sirtori. 71 pages with 25 illustrations. Fidenza, 1953. Tipografia Tito Mattioli.

The authors analyze the several aspects (pathogenetic, anatamohistologic, clinical, and therapeutic) of endometriosis, illustrating with numerous photomicrographs the most interesting and characteristic histologic picture of the cases they have studied. Among these, a case of vaginal endometriosis with a decidual reaction, one of endometriosis in the rectum, a diffuse peritoneal endometriosis with the infiltration of the stroma of a coexistent carcinoma of the sigmoid deserve special mention.

Sulla Necrosi ipofisaria puerperale (Necrosis of the Hypophysis Post Partum). By Filippo Destro. 23 pages with 8 illustrations. Fidenza, 1953, Tipografia Tito Mattioli.

The author describes a case of hemorrhage caused by placenta previa and accompanied by necrosis of the hypophysis brought about by autochthonous thrombosis of the vessels, concerning mainly the front and rear lobes.

The sudden onset of a serious polyuria was the clinical symptom which led to the diagnosis of necrosis of the hypophysis, later confirmed by autopsy and histological examinations.

The fact is stressed that, while the absence or disappearance of lactation is a precocious symptom of necrosis of the hypophysis, the presence of polyuria is a precocious symptom of necrosis of the posthypophysis.

A discussion follows on the pathogenesis of the necrosis of the hypophysis.

Sulla distribuzione ed i caratteri istochimici delle mesomucine dell'ovaio e sul loro comportamento mei processi fisiologici e patologici dell'ovulazione (The Distribution and Characteristics of the Histochemical Mucoids of the Ovary and Their Role in the Physiological and Pathological Processes in Ovulation). By F. Destro. 28 pages with 15 illustrations. Fidenza, 1953. Tipografia Tito Mattioli.

The author describes the distribution and the histochemical characteristics of the mucoids of human and rabbit ovary, discussing the meaning of the modifications noted in various conditions of ovarian physiopathology.

In particular, he points out the attitude of the stromal mucoids in the process of ripening and fall of the follicle, in the pathological processes of the ovulation (delay in ripening, polycystic degeneration, etc.), in the process of atresia, stressing the important part that the stromal mucoids play in the determination of these processes.

He finally deals with the histochemical nature, and with the origins of the single mucoid portion of the ovary, establishing their histochemical characteristics, and pointing out their meaning mainly in respect to the biochemical mechanism of fecundation.

Le Discheratosi Della Vulva (Dyskeratosis of the Vulva). By M. Goisis and F. Destro. 26 pages with 11 illustrations. Fidenza, 1953, Tipografia Tito Mattioli.

The authors have been investigating the subject of vulvar dyskeratosis, regarded as a precancerous lesion. After a short survey of such data as are available in the existing literature about the anatomopathological and clinical peculiarities of leukoplakia and kraurosis, they concentrate on attempts to supply an interpretation of these lesions with respect to etiology, pathology, and genetics.

They also describe certain histological images wherein the coexistence of dystrophic and cancerous lesions appears evident.

They conclude by stressing the need for an accurate bioptical investigation in all forms of vulvar disease before starting any treatment whatsoever.

Glandular Physiology and Therapy. A Symposium. Fifth edition. 611 pages with 17 figures and 36 tables. Philadelphia, 1954, J. B. Lippincott Company. $10.00.

This is an outstanding contribution to the field of endocrinology. The thirty-one authors are authorities on the subjects discussed, and each one commands respect in the field of endocrinology about which he writes. The book is easy to read, not only because of the print but also especially because of the lack of disturbing glare from its unglazed paper.

The material in each chapter is most complete and, in general, well presented. There is more hormonal physiology than therapy although the latter is fairly well covered. The material is presented in the light of present-day knowledge and is not a rehash of past information. Some of the subjects discussed quite fully are often treated lightly in other works on endocrinology. Thus, ''Abnormalities of Body Weight'' and ''Endocrine Management of Neoplastic Disease'' are most adequately covered.

The chapter on ''Physiology of Menstruation and Circulation'' is one of the most complete known to the reviewer. This portion of the book could well be required reading not only for endocrinologists but also for all obstetricians and gynecologists.

An important feature is the large and current bibliography at the end of each subject discussed.

This book should be well received and find a place in the libraries of those interested in endocrinology and also should serve as a source of reference for those who handle an occasional case of hormonal disturbance.

Office Gynecology. By J. P. Greenhill. 517 pages with 127 illustrations. Chicago, 1954, The Year Book Publishers, Inc. $7.75.

This text has been written for the general practitioner and gynecologist. The book has been thoroughly revised and contains a wealth of gynecological detail condensed into 517 pages, and is well indexed and illustrated. The subject matter is systematized and covers every imaginable facet of gynecology. There is an outline of necessary office equipment, a discussion of self-examination of the breast, a chapter on sterility and fertility, a chapter on stress incontinence, a discussion of psychosomatic gynecology, and a rather detailed presentation of prenatal examination and advice.

This text is to be recommended as a thorough, compact guide to the clinical practice of gynecology.

Items

Society for Study of Fertility

The Annual Conference of the Society for the Study of Fertility will meet June 23 and 24, 1955, at Birmingham, England. The Secretary is H. H. Fouracre Barns, 31 Weymouth St., Portland Place, W. 1, London, England.

International Federation of Gynecology and Obstetrics

The International Federation of Gynecology and Obstetrics was founded during the International Congress on Gynecology and Obstetrics in Geneva, July 26 to 31, 1954. The Executive Secretary is Dr. W. Geisendorf, Geneva, Switzerland.

American Board of Obstetrics and Gynecology

The next scheduled Examinations (Part II), oral and clinical for all candidates, will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 12 through May 20, 1955. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

ROBERT L. FAULKNER, M.D., Secretary
2105 Adelbert Road
Cleveland 6, Ohio